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Draft Criteria Document for Tetrachloroethytlene

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DRAFT CRITERIA DOCUMENT FOR TETRACHLOROETHYLENE

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CRITERIA AND STANDARDS DIVISION
OFFICE OF DRINKING WATER
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16. ABSTRACT

This document summarizes the health effects of Tetrachloroethylene. Topics include: General Information and Properties; Human Exposure; Pharmacokinetics; Health Effects in Animals and Humans; Mechanisms of Toxicity; Risk Assessment and Quantification of Toxicological Effects.

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I. SUMMARY

Tetrachloroethylene is a colorless, nonflammable liquid that is an excellent solvent for many organic substances. It is used extensively in the dry cleaning industry and as a metal degreaser and intermediate in the synthesis of certain types of fluorocarbons.

Tetrachloroethylene can be absorbed via ingestion, inhalation or through the skin. The results of pharmacokinetic studies suggest that, in the human, 25-60% of an inhaled dose is absorbed and retained at doses where no equilibrium has been established. Continued exposure results in the exhalation of nearly all of the tetrachloroethylene unchanged. Only 1-2% is excreted in the urine, principally as trichloroacetic acid and trichloroethanol. Metabolism and excretion are relatively slow, the half-life of unchanged tetrachloroethylene in the exhaled breath being 65 hours. The urinary half-life of total trichloro metabolites averages 144 hours after an 8 hr/day, 5 day/week exposure to 30-100 ppm. Tetrachloroethylene is lipophilic and redistributes rapidly to the body's fat stores. The estimated half-life in body fat is about 72 hours.

Because of its lipophilicity, tetrachloroethylene tends to accumulate in tissues with high fat content. After exposure ceases, release of the substance from body fat stores persists for an extended period, thereby prolonging the potential exposure to and toxicity of tetrachloroethylene.

In animals, the most characteristic effect of acute high level exposure to tetrachloroethylene is on the central nervous system. It is manifest, at increasing concentrations, as depression, ataxia, unconsciousness, respiratory and cardiac arrest and death.

As the dose increases, fatty infiltration of the central areas of the liver and then necrosis develop. Renal damage is seen at doses above which initial liver damage occurs. Both a depression and an elevation of total hepatic lipids have been reported, but evidence favors elevation. Liver triglycerides have also been shown to increase, concomitant with a decrease in hepatic ATP.

Additional changes reported, but requiring confirmation and validation, include morphological changes in mast cells indicating a stress response, alterations in serum protein ratios and increased bile duct-pancreatic flow (a phenomenon of as yet unexplained significance). Also, in the brain, there was reported a diminution of RNA content and an increase in non-specific cholinesterase activity accompanied by sequestering of tetrachloroethylene in body fat and brain tissue, and behavioral changes due principally to the loss of voluntary motor coordination.

Short term/subchronic exposure effects are manifest principally as damage to the liver and kidney. Liver morphology progresses from congestion and cloudy swelling to fatty degeneration and necrosis. Kidney changes progress from an increase in weight, cloudy swelling of the tubular epithelium, desquamation and necrosis. The changes are most often seen at levels higher than those detected to date in the ambient environment.

Other effects observed include stimulation of the adrenals, aberrancies in the electroencephalogram (EEG) indicating subtle central nervous system (CNS) effects, decrease in electroconductance and contraction of voluntary muscle, degeneration of the germinal epithelium of the testis, congestion of the spleen and depression of growth.

Longer-term (up to lifetime) exposure in animals has been reported to result principally in the previously-described hepatic and renal damage. Body weight gain can be thwarted. In addition, it has been suggested that low inhalation exposure levels (15 ppm) may affect the immune system in such a way as to reduce antibody titers and increase phagocytic activity. Unconfirmed evidence of anemia in a population of female rats and a possible leukopenia have been suggested. Again, subtle CNS effects have been reported, both physiological and morphological.

As with other animals, the most characteristic response in humans to an acute exposure to tetrachloroethylene is depression of the central nervous system. While anesthetic concentrations can be reached in the inspired air, few deaths could be documented as having been due to tetrachloroethylene exposure. All narcotic symptoms appear to be reversible. Transient liver and kidney dysfunction has been noted in some cases.

Reported short term/subchronic occupational or accidental exposures usually consist of repeated exposures over several months resulting in periods of apparent CNS depression, usually without narcosis. Symptoms often manifested are inebriation, dizziness, fatigue, anorexia and insomnia. The effects reverse within munutes to hours after the exposed individual is removed from contact with the substance. With higher levels of exposure, hepatic toxicity can be expected. Liver changes may take several months to revert to normal.

Upon chronic exposure, the likelihood of chronic nervous system damage increases. Although not well-documented to date, a few case reports suggest that permanent neuropathies may result from long-term exposure to tetrachloroethylene. Hepatic damage can be persistent. It has been suggested that tetrachloroethylene can induce diseases such as Raynaud's phenomenon or the complex of symptoms observed in workers exposed to vinyl chloride. Occasional idiosyncratic responses such as pulmonary edema, bronchial asthma, hypersensitivity or dependency have been reported.

Few epidemiologic studies are available from which definitive conclusions concerning the long-term effects of tetrachloroethylene can be made. Some studies are complicated by the fact that the individuals under study have been exposed to other structurally-similar solvents, either previously or coincidentally. A preliminary report on the mortality profile of dry cleaning workers suggested that there is an excess of certain kinds of cancers in the exposed population. However, greater consideration of confounding factors must be given before a cause/effect relationship can be established between exposure to tetrachloroethylene and the increase in incidence of cancer.

The odor threshold in air for tetrachloroethylene is 50 ppm for previously-unexposed individuals. With increasing exposure, both in terms of duration of a single exposure and numbers of repeated exposures, the threshold for detection rises.

The only reported experience with tetrachloroethylene exposure by the oral route is its use as an anthelminthic. The few reported studies of wide-scale use for the treatment of hookworm and other gastrointestinal infestations suggest that the substance is relatively innocuous by the oral route. However, a host no-effect level for oral exposure cannot be derived from these relatively old clinical reports.

A well-controlled study of the effects observed over a range of acutely-applied vapor concentrations of tetrachloroethylene was that of Rowe, et al. (1952) in which the investigators exposed volunteers to increasing average concentrations of 100 to 1060 ppm. Subjective and objective responses were noted. Slight discomfort was observed at the lowest dose in one of six individuals. Doubling the initial concentration resulted in sinus congestion in all subjects. Tripling the initial concentration was discomfiting to all, each of whom suffered CNS depressant effects of lightheadedness, inebriation, etc. Stewart and his coworkers have suggested that behavioral changes may take place at concentrations equivalent to the present OSHA standard of 100 ppm. Reevaluation of this standard may be necessary. In July 1976, NIOSH recommended that the exposure limit be reduced to 50 ppm (time-weighted average for up to a 10-hour workday, 40-hour work week) (NIOSH, 1976; 1978a). In 1981, the ACGIH announced its intent to reduce the TLV to 50 ppm (335 mg/m^3).

The majority of mutagenicity studies revealed no evidence of mutagenic activity by tetrachloroethylene. Two positive reports in Salmonella have been published; in one, it is unclear as to whether the tetrachloroethylene was pure or contained stabilizing substances. In the other, only the stabilized chemical was positive; the unstabilized substance was negative.

Under the conditions of the NCI bioassay published in 1977, tetrachloroethylene was concluded to be a liver carcinogen in B6C3F1 mice of both sexes, but not in Osborne-Mendel rats. The bioassays were marred by numerous technical flaws and are interpreted by many to be inconclusive and unconvincing. Other bioassays, using revised and refined experimental protocols, are underway, with some nearing completion. Data from these studies should provide more substantial evidence on the compound's potential for carcinogenicity.

Based upon the assumption that the NCI bioassay, in fact, reflected positive carcinogenicity, the National Academy of Sciences (NAS) and EPA's Carcinogen Assessment Group (CAG) have calculated projected incremental excess cancer risks associated with the consumption of tetrachloroethylene via drinking water. These risk estimates are summarized in Table IX-1.

II. GENERAL INFORMATION AND PROPERTIES

Tetrachloroethylene (perchloroethylene; PCE; 1,1,2,2-tetrachloroethylene) is a colorless, nonflammable liquid with a pleasant odor. Certain of its physical properties are listed in Table II-1.

TABLE II-1

Structural Formula:	$Cl_2C=CCl_2$
Molecular Weight:	165.85
Melting Point:	-23.4°C
Boiling Point:	121.2°C
Solubility in Water:	150 mg/l (25°C)
Solubility in Octanol:	Highly soluble
Octanol/Water Coefficient	339
Log Partition Coefficient Octanol/Water	2.86
Partition Coefficient Water/Air	1.22 (20°C)
Vapor Density:	5.8 gm/l (760 mm Hg and 121.2°C)
Vapor Pressure:	19 mm Hg
Specific Gravity:	1.623

1 mg/l=147.4ppm; 1 ppm=6.78 mg/m³ (25°C; 760 mm Hg)

Adapted from Patty (1963).

The odor threshold for PCE in air is about 300 mg/m^3 or about 50 ppm (Carpenter, 1937). The odor threshold for tetrachloroethylene in water is 0.3 mg/kg or approximately 300 ug/l (Kolle, et al. 1972).

Tetrachloroethylene is the most chemically stable (thermally and photolytically) of the chlorinated ethanes and ethylenes. It is stable to about 500 °C in the absence of catalysts, moisture or oxygen. The unstabilized compound will decompose slowly to trichloroacetic acid and hydrochloric acid if allowed to come into contact with moisture (Fuller, 1976).

PCE undergoes photodegradation in sunlight, with a half-life of two days, yielding free chlorine, HCl and trichloroacetic acid (Moolenaar, 1975, cited in Fuller, 1976). When irradiated with ultraviolet light in the presence of oxygen, tetrachloroethylene undergoes autooxidation to trichloroacetyl chloride and phosgene, a substance of significant toxicity. Singh et al. (1975) performed experiments which showed that irradiation of tetrachloroethylene in air for 7 days led to the formation of about 8% (by weight) carbon tetrachloride (CCl_4) and 70 to 85% phosgene ($COCl_2$).

Tetrachloroethylene is an excellent solvent for many types of organic substances. This characteristic has led to its widespread use in the dry cleaning industry and as a metal degreaser in many types of industries. It has also been used as an intermediate in the synthesis of certain types of fluorocarbons (Fuller, 1976).

In 1974, 3.7 x 10^5 tons were produced in the United States, out of a world production capacity of about 10^6 tons (Fuller, 1976). Over half of the domestic market is in the textile industry. More than 50% of the dry cleaning stablishments in the U.S. use tetrachloroethylene at least 80% of the time.

III. PHARMACOKINETICS

Absorption/Uptake

Tetrachloroethylene can be absorbed following ingestion, inhalation, and to a lesser degree, by dermal exposure. Schwander (1936) reported that a rabbit absorbed it to a moderate extent through the skin; some portion was excreted via exhalation within the first hour of a 4.5 hour dermal exposure. In studies on rabbit skin, Rowe et al. (1963) used dermal doses of up to 30 g/kg. Since the concentrated form was used, the doses produced chemical burns but no lethality, suggesting low skin penetration and absorption.

A study of the absorption of PCE vapor through intact human skin (Riihimaki and Pfaffli, 1978) demonstrated that only insignificant amounts of the chemical would be absorbed at exposure levels of 600 ppm for 3.5 hr (pulmonary absorption was experimentally eliminated). Using the blood and exhaled air values, it was calculated, assuming 98% alveolar excretion, that about 1.1% was absorbed. PCE exhalation displayed three distinct half-times: 1 hour (first two hours post-exposure), 6 hours (three to eight hours of post-exposure), and 72 hours (> eight hours post-exposure).

Stewart and Dodd (1964) exposed five human subjects to pure tetrachloroethylene by immersing one thumb in the solvent for 40 minutes. Concentrations were measured in the breath during and after exposure. The compound penetrated human skin more slowly and was eliminated more slowly from the body than the other substances studied (carbon tetrachloride, methylene chloride, trichloroethylene and methyl chloroform) Peak breath concentration was not achieved until nearly an hour after initiation of exposure. In contrast, peak breath concentration for the other substances tested was reached within thirty minutes. The subjects were still exhaling half the peak breath concentration nearly ten hours after initiation of exposure to tetrachloroethylene. The equivalent half-times for the other chemicals ranged from slightly over one hour for methylene chloride to about two hours for carbon tetrachloride. The subjects reported a mild burning sensation 5 to 10 minutes after immersion, the intensity of which increased to a moderate burning sensation within 15 to 20 minutes. The sensation continued for 10 minutes after removal from the bath and subsided gradually within an hour; the accompanying marked erythema subsided within 1 to 2 hours after exposure. The highest mean peak breath concentration (0.31 ppm) occurred within 15 minutes after completing a 30-minute dermal exposure. Five hours after exposure, the mean breath concentration was 0.20 ppm. The authors suggested that an estimate of the amount of solvent absorbed through the skin could be made by comparing the postabsorption alveolar breath "decay" curves with "decay" curves obtained following controlled human exposures to known vapor concentrations of the solvent. From this comparison, it can be observed that the amounts absorbed during dermal exposure over a 30-minute period would be similar to the amount absorbed following a 30-minute inhalation exposure at 2-5 times the peak breath concentration recorded (0.31 ppm).

Using inhalation exposure, Stewart, et al. (1961b) found that PCE appeared to be approaching steady-state levels in venous blood of human volunteers with 3 hours of continuous exposure at 194 ppm. Such results suggest a rapid attainment of steady-state levels of PCE within the body. This may be deceptive, however, since the biological half-life of PCE metabolites (measured as total trichloro compounds) is 144 hours (Ikeda and Imamura, 1973). The relative stability of PCE concentrations in blood beyond 2 hours probably represents a redistribution phenomenon common to a number of volatile anesthetics (Goodman and Gilman, 1966). Studies by Stewart, et al. (1970) have shown that PCE concentrations in expired air immediately following exposure to 100 ppm for 7-8 hours daily increased with repeated exposures over a five-day period. A state of equilibrium was never achieved during the exposure period. These data suggest that a steady-state implied by the leveling off of venous blood PCE concentrations is not reached with short-term exposures.

Morgan, et al. (1970) attempted to determine the retention rate of several aliphatic halogenated hydrocarbons following inhalation of a single dose (approximately five mg.). The compound of interest was labelled with ^{38}Cl. The volunteer inhaled the vapor deeply and held his breath for 20 seconds to allow for maximum retention. After administration, the subject continued to breathe room air, but exhaled into a trap filled with granular charcoal. This procedure continued for about an hour, with the traps being changed initially at two-minute intervals, then at 10-minute intervals. Five minutes after exposure, tetrachloroethylene was being excreted at a rate of 0.6%/minute; this rate had slowed to slightly over 0.1% per minute at one hour. About 15% of the inhaled dose had been exhaled at this time. In addition, a urine sample was taken one hour after the single breath of PCE. The ^{38}Cl activity was measured. The excretion rate for PCE metabolites was shown to be less than 0.01%/minute under these experimental conditions. No attempt was made to identify the nature of the radioactive material; thus, no conclusion can be made as to what substances were being excreted.

Monster and co-workers published a series of reports in which the characteristics of tetrachloroethylene uptake and retention were studied. In the first of these (Monster, et al. 1979), six male volunteers were exposed for 4 hours to 72 ppm tetrachloroethylene at rest, to 144 ppm at rest, and to

142 ppm at rest combined with a work load. Minute volume and concentrations in exhaled air were measured to estimate the uptake. Concentrations of PCE and trichloroacetic acid (TCA) were determined in venous blood. Exhaled air was analyzed for PCE and urine for TCA. The uptake/min decreased in the course of the exposure to 60% of the initial uptake. The total uptake was influenced more by (lean) body mass than by respiratory minute volume or adipose tissue. During work load, the uptake and minute volume increased to three times the value at rest. In the post exposure period, the quotient of the blood concentrations and exhaled air concentrations of PCE remained nearly constant at 23. Following exposure, about 80-100% of the uptake was excreted unchanged by the lungs, whereas until 70 hours after exposure, the amount of TCA excreted in urine represented about 1% of the uptake.

In the second report (Monster, 1979), the author showed that PCE has a high blood/air partition coefficient (15). This was determined by comparing the concentration of the solvent in peripheral venous blood with the concentration in expired air at the end of the exposure. This is reflected by the rapid uptake during the initial stages of exposure. However, metabolism was insignificant (2%) and therefore, the amount taken up per minute decreased over the course of exposure. In the third report (Monster and Houtkooper,1979) the authors studied the precision by which one could estimate the individual uptake of a compound from measured biological parameters after exposure. With simple linear and multiple linear regression analysis, the individual uptake of tetrachloroethylene was estimated from the concentrations of solvent and its metabolites in biological media (blood, urine, exhaled air) at 2 hours and at 20 hours after exposure. The best results were obtained by estimation from the concentrations in blood, particularly of the solvent itself. Inclusion of results of simultaneously measured concentraitions in exhaled air or urine did not improve the estimate.

Few data are available which determine the percentage uptake of ingested tetrachloroethylene. Studies on the pharmacokinetics of orally-administered tetrachloroethylene are needed. Lamson, Robbins and Ward (1929) stated that in ingested food, the presence of fat was required for tetrachloroethylene absorption through the intestine of dogs. However, the chemical (in concentrations sufficient to produce narcosis) was absorbed by rats and mice, and to a lesser extent in cats and puppies, without the presence of fat. Daniel (1963) showed that nearly 98% of a single oral dose of ^{36}Cl-tetrachloroethylene (189 mg/kg) to the rat was excreted in the expired air, while only 2% was excreted in the urine. Thus, virtually all of the dose was absorbed.

Distribution. Once in the bloodstream, PCE tends to distribute to body fat. Although the human data available are quite limited, in those individuals which have significant body burdens (subjects E and F in Table III-1), ratios of fat to liver concentrations are greater than 6:1 (McConnell, et al., 1975).

A more marked distribution of PCE in fat is observed using controlled exposures to rats. The data in Table III-2 (Savolainen, et al. 1977) were obtained from animals who had been exposed to 1,340 mg PCE/m^3 for 6 hours/day on 4 prior days. The zero time values represent the residual PCE from these previous exposures on the 5th day. Each succeeding time interval indicates the kinetics of PCE buildup in each organ with the identical exposure conditions on the 5th day. As can be seen in the table, a substantial residual concentration of PCE is found in fat from the previous exposures. PCE levels rise more or less continuously with duration of exposure in brain, lungs and fat, but tend to level out in blood and liver after a 3-hour exposure. It is notable that brain concentrations of PCE exceed blood levels by about fourfold, independent of duration of the exposure. On the other hand, the ratio of the concentration in fat relative to blood decreases from near 150:1 before exposure on the fifth day to 50:1 over the course of exposure on the fifth day. These data suggest that turnover of PCE in fat is slower than that observed in other tissues.

The results of Monster (1979) show further that tetrachloroethylene will distribute rapidly from blood into the

TABLE-1

DISTRIBUTION OF TETRACHLOROETHYLENE IN HUMAN TISSUE AT AUTOPSY (McCONNELL, ET AL. 1975)

CONCENTRATIONS IN UG/KG (WET TISSUE)

Subject	Age	Sex	Tissue	Tetrachloroethylene
A	76	F	Body fat	6
			Kidney	<0.5
			Liver	<0.5
			Brain	<0.5
B	76	F	Body fat	1
			Kidney	6
			Liver	2
			Brain	<5
C	82	F	Body fat	0.4
			Liver	1.2
D	48	M	Body fat	0.8
			Liver	0.7
E	65	M	Body fat	21
			Liver	3.4
F	75	M	Body fat	29.2
			Liver	4.3
G	66	M	Body fat	0.5
H	74	F	Body fat	4

TABLE III-2

CHANGES IN THE ORGAN CONTENT OF PCE WITH DURATION OF EXPOSURE IN RATS HAVING PRIOR HISTORY OF PCE EXPOSURE

Duration of Exposure (h)	Concentration*					
	Cerebrum	Cerebellum	Lungs	Liver	Perirenal Fat	Blood
0	3.1 ± 0.6	2.2 ± 0.7	1.6 ± 0.3	5.8 ± 1.5	103 ± 3	0.7 ± 0.2
2	14.9 ± 2.8	10.3 ± 1.2	7.6 ± 1.7	17.8 ± 4.5	162 ± 29	3.5 ± 0.7
3	18.0 ± 0.8	12.0 ± 0.7	8.7 ± 1.6	22.4 ± 0.2	134 ± 6	4.2 ± 0.2
4	16.8 ± 2.9	11.3 ± 0.9	9.9 ± 2.2	22.2 ± 0.1	183 ± 32	4.1 ± 0.6
6	23.7 ± 1.2	15.3 ± 0.3	12.2 ± 0.6	26.7 ± 4.0	286 ± 70	5.0 ± 1.1

*ug/g wet weight of tissue or ug/ml blood ± range of two animals.

From: Savolainen, et al.(1977)

tissues, especially fat. While the blood/gas coefficient was shown to be about 15, the fat/blood ratio was determined to be 90. Therefore, the capacity of adipose tissue to take up tetrachloroethylene is high. In addition, at a given solvent concentration in the blood, the half-life for saturation of the fat to 50% of its equilibrium concentration is about 25 hours for PCE compared with about 15 hours for methyl chloroform.

Retention/Biological Half-life. Stewart et al. (1961a) postulated a long biological half-life and a rapid blood clearance for tetrachloroethylene because humans exposed to the compound at 194 ppm for either 83 or 187 min or at 101 ppm for 183 minutes had no detectable levels in their urine or blood after 30 minutes. Ninety-four hours were required for clearance of the vapor from the expired air after an 83 minute exposure at 194 ppm; 400 hours were needed after a 393 ppm exposure for 210 minutes.

Morgan et al. (1970, 1972) also have shown that the elimination rate of a chlorinated hydrocarbon such as tetrachloroethylene is related to its lipid solubility. In the 1970 study, the authors determined the blood/gas partition coefficient to be 9 *in vitro* at 40°C. In their 1972 study, the serum/gas partition coefficient (K_D) determination was repeated with some minor modifications in the experimental procedure, including a temperature decrease to 25°C. Under the new experimental conditions, the K_D was shown to be 32. A known quantity of tetrachloroethylene vapor labelled with

^{38}Cl was introduced into a flask containing freshly drawn venous blood or serum. After a short equilibration period, the radioactivity in the liquid and gaseous phases was counted. Differences in the techniques employed by this group and Monster (1979) can account for the differences in the partition coefficients as determined by each. Comparison of this result with those for other halogenated compounds studied showed that the K_D appears to increase with an increase in the number of chlorine atoms for derivatives of methane, ethane and ethene. The results also showed that during prolonged exposure, compounds with high lipid solubility, such as tetrachloroethylene, will accumulate more rapidly with higher tissue levels resulting. When exposure is terminated, the highly lipid soluble substances will be eliminated more slowly.

Fernandez et al. (1976) also stated that tetrachloroethylene was eliminated primarily via expired air and that very little was metabolized by humans. In fact, two weeks were required to eliminate completely the tetrachloroethylene retained during an 8-hour exposure to 100 ppm of the chemical.

Bolanowska and Golacka (1972), in a preliminary report, showed that humans exposed to tetrachloroethylene at 390 mg/m^3 (56 ppm) for 6 hours with two half-hour interruptions eliminated 25% of the absorbed chemical via expired air, 0.02%/hr percutaneously, less than 10% via the urine and retained 62% in their bodies. For the first few days after cessation of exposure, tetrachloroethylene disappeared from the breath with a half-time of about 70 hours. They presumed the absorbed percentage of the dose underwent biotransformation in the body. A major metabolite, however, trichloroacetic acid, accounted for only 2% of the inhaled tetrachloroethylene over a 67-hour collection period.

Ikeda and Imamura (1973) reported that the half-time of tetrachloroethylene in humans as measured by urinary excretion of metabolites was 144 hours, after exposure 8 hours/day, 5 days/week, at 10 to 100 ppm.

Experimentally, Stewart et al. (1970) showed that the breath excretion of tetrachloroethylene increased only 10% on the second day of exposure. On the average, when 100 ppm was inhaled for seven hours, the breath concentration was 20 ppm. Using the methods of Bolanowska and Golacka (1972) for calculating tetrachloroethylene kinetics, it was determined that alveolar excretion occurred at the rate of 15 mg/hr after a 6-hour exposure to 390 mg/m^3 (about 56 ppm).

Tada and Nakaaki (1969) stated that after exposure to tetrachloroethylene, the net excretion of the metabolite trichloroacetic acid in the urine increased daily to a maximum in 3 or 4 days.

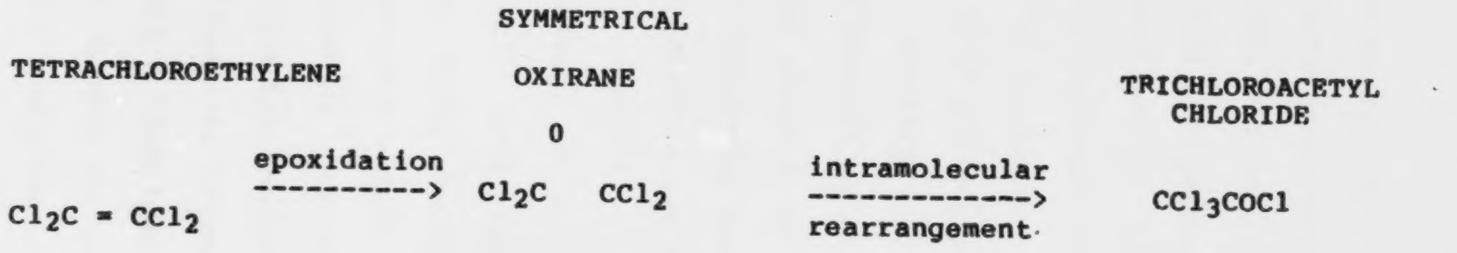
Van Dyke and Wineman (1971), using rat liver microsomes in a closed incubation system, found that less than 1% of the ^{36}Cl was enzymatically removed from ^{36}Cl-labeled tetrachloroethylene in 30 minutes thereby indicating a very slow degradation period.

Metabolism. In a qualitative sense, metabolic products appear to be similar in humans (Ikeda, et al. 1972; Ikeda, 1977) and experimental animals (Yllner, 1961; Daniel, 1963; Ikeda and Ohtsuji, 1972). The metabolic pathway is summarized in Figure III-1. A similar reaction has been observed when PCE is exposed to oxygen, excess chlorine, and sunlight at 36 to 40°C (Frankel, et al. 1957).

Ogata, et al. (1971) reported that 1.8 percent of the PCE retained by humans was converted to trichloroacetic acid and 1.0 percent to an unknown metabolite in 67 hours. In animals, metabolism of PCE is apparently saturable, in that exposures exceeding 70 mg/m^3 (< 15 ppm) do not increase excretion of trichloroacetic acid in the urine (Ikeda, 1977). However,metabolism of PCE is inducible by phenobarbital (Ikeda and Imamura, 1973) and Aroclor 1254 (Moslen, et al. 1977), suggesting that a higher percentage of metabolic conversion is possible under certain conditions. Moslen and coworkers pretreated rats with phenobarbital or Aroclor-1254 which are inducers of the mixed function oxidase system, followed by one oral dose of 0.75 ml/kg tetrachloroethylene. A significant increase in the urinary excretion of total trichlorinated compounds and trichloracetic acid (tetrachloroethylene metabolites) resulted, giving evidence for involvement of the mixed function oxidase system of liver microsomes in the *in vivo* metabolic pathway. Tetrachloroethylene was metabolized primarily to trichloroacetic

Figure III-1

METABOLIC ROUTE PROPOSED FOR TETRACHLOROETHYLENE



TETRACHLOROETHYLENE $Cl_2C = CCl_2$ $\xrightarrow{\text{epoxidation}}$ SYMMETRICAL OXIRANE $\overset{O}{Cl_2C \quad CCl_2}$ $\xrightarrow[\text{rearrangement}]{\text{intramolecular}}$ TRICHLOROACETYL CHLORIDE CCl_3COCl

REPORTED METABOLITES

OXALIC ACID
$C_2H_2O_4$ o 2 H_2O (Rodents)

DICHLOROACETIC ACID
$CHCl_2COOH$ (Mice)

ETHYLENE GLYCOL
$HOCH_2CH_2OH$ (Rats)

TRICHLOROETHANOL
CCl_3CH_2OH (Man)
(Rodents)

UNKNOWN
CHLORINATED
PRODUCTS

TRICHLOROACETIC ACID
CCl_3COOH

From:
Greim et al. (1975)
Ikeda and Ohtsuji (1972)
Yllner (1961)

acid. Urinary metabolites increased five to seven-fold over controls in phenobarbital- and Aroclor-treated groups. Aroclor pretreatment enhanced the toxicity of tetrachloroethylene. SGOT levels were doubled and histological liver lesions were more severe in Aroclor-pretreated, tetrachloroethylene-dosed rats. The authors concluded that the magnitude of cytochrome P-450 induction correlated with the extent of liver damage by tetrachloroethylene, strongly suggesting that a tetrachloroethylene metabolite is involved in the liver effects.

Exposure of five female mice to ^{14}C-PCE vapor (1.3 mg/g body weight) in a sealed flask for 2 hours resulted in 90% absorption of the solvent; during subsequent 4-day measurements, 70% was expired in the air, 20% was excreted in the urine and 0.5% was excreted in the feces (Yllner, 1961). Fractionation of urinary metabolites resulted in the identification of trichloroacetic acid (52%), oxalic acid (11%), dichloroacetic acid (trace) and other unidentified, polar labeled compounds (18%). Monochloroacetic acid, formic acid and trichloroethanol were not identified as metabolities. Therefore, a metabolic pathway in which tetrachloroethylene was converted to trichloroacetic acid via an epoxide intermediate was postulated.

Studies by Daniel (1963) confirmed a similar pathway in Wistar rats which had been dosed by stomach tube with 1.75 or 13 uc of ^{36}Cl-labeled tetrachloroethylene (189 or 1394 mg/kg). At the lower dose level, 97.9% of the ^{36}Cl had been recovered in the expired air after 48 hours; the half-life of respiration for the compound was about 8 hours. The expired air contained no metabolites of tetrachloroethylene and, after 18 days, the urine contained only 2% of the ^{36}Cl, of which 0.6% was trichloroacetic acid. At the higher dose, 1.6% of the radioactivity was recovered in the urine. The level in expired air was not reported. This investigator concluded that the compound was transformed to trichloroacetic acid via an epoxide intermediate. The absence of trichloroethanol and oxalic acid was explained by the fact that the acid chloride is rapidly hydrolyzed to trichloroacetic acid and chloride ion.

The metabolism of tetrachloroethylene in humans, rats, and mice was compared by Ikeda and Ohtsuji (1972). After inhalation exposure, trichloroethanol and trichloroacetic acid as well as other unidentified trichloro compounds were found in the urine of exposed subjects as summarized in Table III-3.

In the Ikeda and Ohtsuji study, rats and mice were also injected intraperitoneally with the chemical (2.7 mmoles/kg body weight) to eliminate the possibility of variation in results due to differences in the efficiency of pulmonary uptake. In these studies, a metabolite profile similar to that observed after inhalation was noted, except that less trichloroethanol was found.

Ikeda et al. (1972) have measured the exposure and subsequent urinary excretion of tetrachloroethylene metabolites in 85 male workers using it as a dry cleaning solvent. In

Table III-3

EXCRETION OF URINARY METABOLITES BY HUMANS, RATS AND MICE AFTER EXPOSURE TO TETRACHLOROETHYLENE

Species	No. Subjects	Exposure Route	Dosage	Urinary metabolites Trichloroacetic acid	 Trichloroethanol
Human[a]/	4	Inhalation	20-70 ppm	4-20 mg/l	4-35 mg/l
Human	66	Inhalation	200-400[b]/ ppm	21-100 mg/l	32-97 mg/l
Rat	48	Inhalation	200 ppm/8 hr	5.3 mg/kg body weight	3.2 mg/kg body weight
Mouse	20	Inhalation	200 ppm/8 hr	20.7 mg/kg body weight	4.3 mg/kg body weight
Rat	35	i.p. injection	460 mg/kg	5.85 mg/kg body weight	0.08 mg.kg body weight
Mouse	20	i.p. injection	460 mg/kg	23.31 mg/kg body weight	0.1 mg/kg body weight

a/ Workers subject to daily intermittent exposure.

b/ Worker receiving 44 ppm was also in direct skin contact with the liquid.

Source: Summarized from the tables of Ikeda and Ohtsuji (1972).

one study, workers exposed 8 hr/day, 6 days/week to 10 to 400 ppm furnished urine samples. A plateau rate of metabolite excretion was reached when the tetrachloroethylene concentration in workplace air approached 100 ppm; this urinary metabolite excretion did not increase even when tetrachloroethylene in the workplace air rose to 400 ppm. The authors concluded that the ability of the human to metabolize tetrachloroethylene is limited, and metabolism patterns differ during acute and chronic exposures. No data were furnished on whether or not larger amounts of tetrachloroethylene are deposited in lipid tissue in the body with increased exposure, but accumulation is implied.

When humans were exposed by inhalation to tetrachloroethylene (87 ppm) for three hours, trichloroacetic acid and unidentified trichloro compounds were found in the urine (Ogata et al., 1971). The concentration of trichloroacetic acid in the urine increased during exposure but returned to nearly normal 64 hours after exposure. The total trichloro compounds recovered in the urine were equivalent to only 2.8% of the retained tetrachloroethylene, 1.8% of this being trichloroacetic acid. Only 4% of the retained dose was metabolized. The concentrations of trichloroacetic acid and the unknown organic chloride were determined by the chromium oxidation method.

Fernandez et al. (1976) have shown that trichloroacetic acid appeared in the urine of humans during exposure and the excretion rate rose slowly although the total urinary excretion after 72 hours was only 1.85% of the total dose retained. Their results are tabulated in Table III-4.

Leibman and Ortiz (1977) studied the enzymatic breakdown of tetrachloroethylene by an in vitro system. They hypothesized that it formed the corresponding oxide, followed by hydration of the oxide to trichloroethylene glycol. Either of these would form only one product, trichloroacetyl chloride, which would rapidly hydrolyze to trichloroacetic acid. Trichloroacetic acid is the only metabolite which has been detected in vitro after tetrachloroethylene liver perfusion. The data suggest that the microsomal drug-metabolizing enzymes are not involved in tetrachloroethylene metabolism to the extent they are in other related compounds (like trichloroethylene). For example, Mg^{++} (at the level which enhances chloral hydrate production by trichloroethylene) will inhibit tetrachloroethylene metabolism. When a key enzyme, epoxide hydrase, was inhibited by adding cyclohexane, no differences in tetrachloroethylene metabolites were seen. This study means that further research is necessary to explain the increased liver toxicity seen in tetrachloroethylene-dosed rats with Aroclor-stimulated enyzme systems, as reported by Moslen et al. (1977).

Table III-4

HUMAN URINARY EXCRETION OF TRICHLOROACETIC ACID [a]

Subject	Time of collection postexposure (hr)	TCA[b] excreted (mg)
E.G.	0-8	4.54
	8-24	7.19
	24-48	9.68
	48-72	3.63
B.H.	0-8	3.05
	8-24	8.50
	24-48	8.95
	48-72	3.70

[a] Exposujres to 150 ppm tetrachloroethylene vapor for 8r.

[b] TCA = Trichloroacetic acid.

Source: Fernandez et al. (1976).

Ikeda (1977) reported on the urinary half-life of tetrachloroethylene metabolites in humans who were occupationally exposed to the vapor. The urinary half-life of total trichloro compounds averaged 144 hours: 190.1 ± 32.9 hours for females (six subjects exposed 8 hr/day, 5 days/week, 10 to 20 ppm) and 123.3 ± 23.5 hours for males (six subjects exposed 8 hr/day, 5 days/week, 30-100 ppm).

The half-life of metabolites expired into alveolar breath was calculated to be 65 hours and for urinary metabolites the mean biological half-life is 144 hours (Ikeda, 1977). Estimated biological half-life for fat stores of tetrachloroethylene is 71.5 hours using the theoretical methods of Guberan and Fernandez (1974).

By two exposure routes, Ikeda (1977) noted that tetrachloroethylene remained in humans about three times longer than trichloroethylene, indicating about a three-fold greater rate of body accumulation of PCE.

A summary of the fate of tetrachloroethylene taken from data in the literature and discussed here is found in Table III-5.

Excretion. PCE itself is eliminated primarily from the body via the lungs (Stewart, et al. 1961a, 1970; Ikeda and Imamura, 1973). The respiratory half-time for PCE elimination has been estimated at 65-70 hours (Stewart, et al. 1970; Bolanskowa and Golacka, 1972; Ikeda and Imamura, 1973).

TABLE III-5

FATE OF TETRACHLOROETHYLENE

				Excretion			
				Unchanged	Metabolized		
Species	Route	Intake	Acutely retained by body (%)	Lung	Urine	Skin	Feces
Man	Inhalation	1 breath (5 mg)		15%/1 hr	2.8%		
Man	Inhalation	87 ppm/3 hr	50	<50%			
Man	Inhalation	194 ppm/187 min		<30 ppm at 1 hr			
Man	Inhalation	390 ppm/6 hr	62	25%	<10%	0.02%	
Man	Inhalation	395 ppm/3.5 hr		85 ppm at 1 hr			
Man	Thumb immersion			Maximum 6.6 ppm			
Mice	Inhalation	1.3 mg/kg		70%	20%		<0.5%
Rats	Inhalation	200 ppm/8 hr			5.3 mg/kg		
Rats	Oral	189 mg/kg and 1394 mg/kg		97.9% (low dose)	1.6-2.1% (18 days)		
Dog	Injection	5.36 g/kg		(2 days)			

Source: U.S. EPA (1979).

Trichloroacetic acid, as a metabolite of PCE, is eliminated with a half-time of 144 hours via the urine (Ikeda and Imamura, 1973). Since the half-time for elimination of trichloroacetic acid as a metabolite of trichloroethylene is only 36 to 58 hours in normal humans, this rate is more a reflection of delayed respiratory turnover of the parent compound than for trichloroacetic acid itself. In all likelihood,this is a result of the greater lipophilicity of PCE relative to trichloroethylene.

Summary

Absorption. From the data available in the series of papers by Monster and co-workers (1979), one can estimate the percentage uptake of tetrachloroethylene by inhalation exposure, by comparing inspired air and blood levels under certain conditions. Adult human males exposed for four hours to 72 to 144 ppm at rest were estimated to have taken up a total of 455 or 945 mg PCE, respectively, or about 25% of the total PCE exposure over the four-hour period.

However, Bolanskowa and Golacka (1972) stated that over 60% of the dose was retained when individuals were exposed by inhalation over the six-hour period with two 30-minute breaks. These values were calculated on the basis of concentrations in inhaled and exhaled air. In addition, Ogata et al. (1971) determined that about half of the dose inhaled was retained, although very little was metabolized subsequently.

Distribution. Tetrachloroethylene has been shown to be highly lipophilic. It has a high blood/alveolar air ratio, and a high fat/blood ratio, suggesting that a substantial amount is sequestered in the body's fat stores. Its release from adipose tissue also is considerably slower than from other body tissues after the termination of exposure. Tetrachloroethylene has been detected in blood, fat, liver, lung, brain and kidney.

Retention. Estimates of the extent of retention of a dose range from 25-60%. That which is retained remains in the body for a long time, relative to other halogenated ethanes and ethylenes. Half-life for the unchanged compound has been determined to be 65-70 hours, and that for the urinary metabolites 144 hours for exposures at concentrations likely to be experienced in the workplace during an average workweek. Higher exposures, for even shorter periods of time, may require 100-400 hours before clearance of PCE from the exhaled breath.

Metabolism. The products that have been identified from the metabolism of tetrachloroethylene in man and other animals are: trichloroacetic acid (man, animals), trichloroethanol (man), organic chlorides (animals), ethylene glycol (rats), oxalic acid (rodents) and dichloroacetic acid (mice). Only small amounts of PCE are metabolized in man (1.8% to TCA and 1% to an unknown substance -- probably trichloroethanol). The metabolic pathway is apparently saturable, at least in animals, as no increase in TCA output is seen with exposures exceeding 70 mg/m^3. However, the half-time for excretion is lengthened, suggesting that the turnover time in the tissues is increased with increased exposure.

IV. HUMAN EXPOSURE

Humans may be exposed to tetrachloroethylene in drinking water, food, and air. Detailed information concerning the occurrence of and exposure to tetrachloroethylene in the environment is presented in another document entitled "Occurrence of Tetrachloroethylene in Drinking Water, Food, and Air" (Letkiewicz et al. 1983). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food, and air.

Exposure Estimation

This analysis is limited to drinking water, food, and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to tetrachloroethylene from sources other than the three considered here, notably in occupational settings and from the use of consumer products containing tetrachloroethylene. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works, and travels, what one eats, and physiologic characteristics related to age, sex, and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various tetrachloroethylene concentrations. The 70-kg male is used for estimating dose, which takes into account the amount of the medium contacted (i.e., water and food ingested; air breathed) and the amount of the tetrachloroethylene actually absorbed into the body.

a. Water

Cumulative estimates of the U.S. populations exposed to various tetrachloroethylene levels in drinking water from public drinking water systems are presented in Table IV-I. The values in these tables were obtained using Federal Reporting Data Systems data (FRDS 1983) on populations served by primary water supply systems and the estimated number of these water systems that contain a given level of tetrachloroethylene. An estimated 11,430,000 individuals (5.3% of the population of 214,419,000 using public water supplies) are exposed to levels of tetrachloroethylene in drinking water at or above 0.5 ug/l, while 874,000 individuals (0.4%) are exposed to levels above 5 ug/l. It is estimated that 105,000 individuals are exposed to levels greater than 60 ug/l. Of the approximately 10.5 million individuals exposed to levels ranging from 0.5 to 5 ug/l, 7 million (67%) obtain water from surface water supplies. All exposure to tetrachloroethylene in drinking water at levels above 5 ug/l is expected to be from groundwater sources.

No data were obtained on regional variations in the concentration of tetrachloroethylene in drinking water. ~~The~~ High~~est~~ concentrations are expected to occur near sites of production and use of tetrachloroethylene. In the case of groundwater, the highest concentrations are expected to occur near waste disposal sites.

Little information was obtained on gastrointestinal absorption rates for tetrachloroethylene. Because of its lipophilic nature, tetrachloroethylene is expected to be readily absorbed. In one study, rats orally exposed to tetrachloroethylene were found to excrete 96% of the administered dose within 72 hours, with 3-4% remaining in the carcass (USEPA 1982). A reasonable estimate for the gastrointestinal absorption of tetrachloroethylene derived from this data is 100%.

Daily intake levels of tetrachloroethylene from drinking water were estimated using various exposure levels and the assumptions presented in Table IV-II. The data in the table suggest that the majority of the persons using public drinking water supplies would be exposed to intake levels below 0.014 ug/kg/day.

An indication of the overall exposure of the total population to tetrachloroethylene can be obtained through the calculation of population-concentration values. These values are a summation of the individual levels of tetrachloroethylene to which each member of the population is exposed. An explanation of the derivation of these values is presented in Appendix C. Population-concentration estimates for tetrachloroethylene in drinking water

Table IV-I. Total Estimated Cumulative Population (in Thousands) Exposed to Tetrachloroethylene in Drinking Water Exceeding the Indicated Concentration

System type	Number of people served in U.S. (thousands)	Cumulative population (thousands) exposed to concentrations (ug/l) of:								
		≥0.5	>5	>10	>20	>30	>40	>50	>60	>70
Groundwater	73,473	4,333	874	440	187	105	105	105	105	0
Surface water	140,946	7,097	0	0	0	0	0	0	0	0
Total	214,419	11,430	874	440	187	105	105	105	105	0
(% of total)	(100%)	(5.3%)	(0.4%)	(0.2%)	(0.1%)	(<0.1%)	(<0.1%)	(<0.1%)	(<0.1%)	(0.0%)

Table IV-II. Estimated Drinking Water Intake of Tetrachloroethylene

Exposure level (ug/l)	Persons using supplies exposed to indicated levels		Intake (ug/kg/day)
	Population	% of Total population	
≥0.5	11,430,000	5.3%	≥0.014
>5.0	874,000	0.4%	>0.14
>10	440,000	0.2%	>0.29
>50	105,000	<0.1%	>1.4
>70	0	0.0%	>2.0

Assumptions: 70-kg man, 2 liters of water/day, gastrointestinal absorption rate of 100% (USEPA 1982).

Table IV-III. Estimated Adult Dietary Intake of Tetrachloroethylene by Food Class[a] Using TEAM Survey Data

	Average intake of food class (kg/day)[b]	Average tetrachloroethylene level (ug/kg)		Average tetrachloroethylene intake (ug/day)	
		Min.[c]	Max.[d]	Min.	Max.
I. Dairy	0.753	0	5	0	4
II. Meat, fish, poultry	0.262	0	5	0	1
X. Fats and oils	0.073	0	13	0	0.95
XII. Beverages	0.128[e]	0	0.5	0	0.06
TOTAL				0	6

[a] Eight food classes not analyzed: grains and cereals (III); potatoes (IV); leafy, legume, and root vegetables (V, VI, VII); garden fruits (VIII); fruits (IX); and sugars and adjuncts (XI).

[b] From FDA 1980.

[c] All nonquantifiable values assumed to be equal to zero.

[d] All nonquantifiable values assumed to be equal to the quantitation limit (value reported is the average of those composites with known quantitation limits).

[e] Calculated by subtracting 14-day drinking water consumption from 14-day beverage consumption (FDA 1980) and dividing by 14.

The U.S. dietary intake was also estimated by assuming that the data on tetrachloroethylene in foods in the United Kingdom (McConnell et al. 1975 cited in Gilbert et al. 1981, Pearson and McConnell 1975 cited in Gilbert et al. 1981 and Versar 1981) are valid in the United States. Average intake was estimated by this method to range between 6-8 ug/day (Table IV-IV). This range is also an approximation, for the following reasons:

1) The data are from Great Britain rather than the United States.

2) The data are limited.

3) Values are averaged without regard to the types and quantities of foods consumed in the United States (e.g., species of fish reported in the studies may represent a negligible portion of the U.S. meat, fish, and poultry group, but are given equal weight in averaging levels of tetrachloroethylene in this food class).

In addition to the available monitoring data, Mara et al. (1979) have provided estimates of atmospheric levels of tetrachloroethylene and the size of the exposed population by applying air dispersion models to several tetrachloroethylene emission sources. The computed average annual concentrations and the size of the populations exposed from each source are presented in Table IV-VI. The data in the table suggest that the majority of the U.S. population is exposed to tetrachloroethylene levels below 340 ng/m^3 (0.34 ug/m^3). This value is somewhat lower than the rural/remote and urban/suburban median values of 1.4 ug/m^3 and 2.3 ug/m^3, respectively, calculated by Brodzinsky and Singh (1982) based on monitoring data.

Table IV-VI also presents population-concentration estimates for tetrachloroethylene. The addition of individual population-concentration estimates results in a combined value of 1.19 x 10^8 ug/m^3 x persons. [It should be noted that this addition may result in some double counting (Table IV-VI)]. Assuming an inhalation rate of 23 m^3 of air/day and a pulmonary absorption rate of 50%, a population-dose of 1.37 x 10^9 ug/day x persons was calculated.

SUMMARY

Table IV-VII presents a general view of the total amount of tetrachloroethylene received by an adult male from air, food, and drinking water. Four separate exposure levels in air, six exposure levels in drinking water, and one exposure level from foods are shown in the table.

The data presented have been selected from an infinite number of possible combinations of concentrations for the three sources. The actual exposures encountered would represent some finite subset of this infinite series of combinations. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to tetrachloroethylene at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

The relative source contribution data for tetrachloroethylene account for differential absorption rates for the chemical by the respiratory and gastrointestinal routes. Thus, relative doses of the chemical directly entering the body are compared. However, it should be noted that the relative effects of the chemical on the body may vary by different routes of exposure.

Table IV-IV. Estimated Adult Dietary Intake of Tetrachloroethylene by Food Class[a] Estimated by Using British Data

		Average intake of food class (kg/day)[b]	Tetrachloroethylene	
			Average level (ug/kg)[c]	Average intake (ug/day)
I.	Dairy	0.753	5	4
II.	Meat, fish, poultry	0.262	2-6	0.5-2
III.	Grains and cereals	0.418	1	0.4
IV.	Potatoes	0.159	0.7	0.1
VIII.	Garden fruits	0.075	1.2	0.09
IX.	Fruits	0.219	2	0.4
X.	Oils and fats	0.073	4	0.3
XII.	Beverages	0.128[d]	3	0.4
	TOTAL			6-8

[a] Four food classes not analyzed: leafy, legume, and root vegetables (V, VI, VII); and sugars and adjuncts (XI).

[b] From FDA 1980.

[c] Average of detectable values in food class (packet tea not included).

[d] Calculated by subtracting 14-day drinking water consumption from 14-day beverage consumption (FDA 1980) and dividing by 14.

Gastrointestinal absorption of tetrachloroethylene was discussed in the previous section. The estimated absorption rate was 100%. Assuming that the average adult weighs 70 kg, the estimated adult dietary intake calculated by using the TEAM study would range from 0-0.09 ug/kg/day. Using the British data, average intake would range from 0.09-1 ug/kg/day. As judged from these two values, daily adult intake of tetrachloroethylene is estimated to be approximately 0.09 ug/kg/day.

It is expected that dietary levels of tetrachloroethylene would vary somewhat with geographical location, with higher levels occurring in foods from areas near sources of tetrachloroethylene. However, because of the limited data available, no estimates of variations in intake by geographical region could be made. Variances in individual exposure due to differences in diet also could not be assessed.

were 1.8 x 10^7 ug/l x persons (best case), 4.5 x 10^7 ug/l x persons (mean best case), 1.4 x 10^8 ug/l x persons (mean worst case), and 1.7 x 10^8 ug/l x persons (worst case).

Assuming a consumption rate of 2 liters of water/day and a gastrointestinal absorption rate of 100%, population-dose values of 3.6 x 10^7 ug/day x persons (best case), 9.0 x 10^7 ug/day x persons (mean best case), 2.8 x 10^8 ug/day x persons (mean worst case), and 3.4 x 10^8 ug/day x persons (worst case) were derived.

b. Diet

The U.S. dietary intake of tetrachloroethylene was estimated using data from the TEAM survey (Pellizzari et al. 1982) on levels of tetrachloroethylene found in various food classes and data on quantities of food consumed daily in each food class (FDA 1980) (Table IV-III). The TEAM study found only five positive samples of 40 tested, and in each case the level observed was below the quantitation limit. The range of tetrachloroethylene in the food classes was calculated by assuming either that the nonquantifiable values for the composite samples equaled zero (minimum estimate) or that they equaled the quantitation limit (maximum estimate). By this method, adult intake of tetrachloroethylene in these foods was estimated as 0-6 ug/day.

Several problems arose in the use of these data:

1) The data are limited, since food samples were obtained on only five occasions, and the foods obtained may not be representative of normal tetrachloroethylene levels in foods. ?

2) In some cases, the quantitation limits were high, so significant levels in some foods may not have been quantified.

3) Only four of 12 food classes, those suspected of containing the highest levels of volatile organics, were analyzed.

4) The composite samples generally contained lower levels of tetrachloroethylene than expected from levels in subcomposite samples (i.e., some tetrachloroethylene appeared to be lost during compositing).

Because of these limitations, the dietary intake range for tetrachloroethylene is considered to be an approximation.

c. Air

Exposure to tetrachloroethylene in the atmosphere varies from one location to another. The highest level of tetrachloroethylene reported in the atmosphere was 220,000 ng/m^3 (220 ug/m^3) (Bozzelli and Kebbekus 1979, Bozzelli et al. 1980, Pellizzari 1977; all cited in Brodzinsky and Singh 1982). High levels, averaging greater than 25,000 ng/m^3 (25 ug/m^3), have been detected in other areas. Normal levels, however, are somewhat lower. Brodzinsky and Singh (1982) calculated median air levels of tetrachloroethylene for rural/remote areas, urban/suburban areas, and source dominated areas of 1,400 ng/m^3 (1.4 ug/m^3), 2,300 ng/m^3 (2.3 ug/m^3), and 4,800 ng/m^3 (4.8 ug/m^3), respectively.

The monitoring data available are not sufficient to determine regional variations in exposure levels for tetrachloroethylene. However, urban and industrial areas appear to contain higher levels. Large releases of tetrachloroethylene would be expected in these areas as a result of dry cleaning and metal cleaning operations.

USEPA (1982) estimated that 50% of tetrachloroethylene inhaled is absorbed into the body system. The daily respiratory intake of tetrachloroethylene from air was estimated using the assumptions presented in Table IV-V and the median and maximum levels for tetrachloroethylene reported above. The estimates in Table IV-V indicate that the daily tetrachloroethylene intake from air for adults in source dominated areas is approximately 0.8 ug/kg/day. In contrast, the intake calculated using the maximum tetrachloroethylene level reported is 36 ug/kg/day; few if any persons are believed to be exposed at that level. The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Table IV-V. Estimated Respiratory Intake of Tetrachloroethylene

Exposure (ug/m^3)	Intake (ug/kg/day)
Rural/remote (1.4)	0.23
Urban/suburban (2.3)	0.38
Source dominated (4.8)	0.79
Maximum (220)	36

Assumptions: 70-kg man, 23 m^3 of air inhaled/day (ICRP 1975), pulmonary absorption rate of 50% (USEPA 1982).

Table IV-VI. Summary of Estimated Population Exposures to Atmospheric Tetrachloroethylene

Source	Population exposed[a]					Compariso among sour (10^8 ug/m person-yea
	Annual average tetrachloroethylene concentration (ug/m^3)					
	0.07-0.34	0.41-0.68	0.75-6.8	6.9-27	Total[b]	
Production facilities	300,000	20,000	5,000	--	300,000	0.07
Dry cleaning:						
Commercial	c	20,000,000	11,000,000	41,000	30,000,000	53
Coin-operated	c	2,600,000	790,000	--	3,000,000	4.1
Industrial	c	2,900,000	1,800,000	4,000	5,000,000	8.2
Metal cleaning	c	20,000,000	11,000,000	120,000	30,000,000	54

[a] Data converted from ppb to ug/m^3 by multiplying by 6.8. A dash (--) signifies that no exposed population was estimated for the annual average concentration listed. There may be some people exposed to those concentrations for shorter periods of time. In addition, the analysis for dry cleaning and metal cleaning operations assumed that no people lived within certain distances of the plant.

[b] Totals are rounded to one significant figure. Population estimates are not additive vertically because double-counting exists, due to overlap of sources.

[c] Not estimated because the closeness of the sources resulted in double-counting of the exposed population.

Source: Mara et al. 1979

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Table IV-VII. Estimated Dose of Tetrachloroethylene Absorbed from the Environment by Adult Males in ug/kg/day (% from Drinking Water)

Concentration in drinking water (ug/l)	Concentration in air Rural/remote (1.4 ug/m^3)	Urban/suburban (2.3 ug/m^3)	Source dominated (4.8 ug/m^3)	Maximum (220 ug/m^3)
0	0.32 (0%)	0.47 (0%)	0.88 (0%)	36 (0%)
0.5[a]	0.33 (4.2%)	0.48 (2.9%)	0.89 (1.6%)	36 (0.04%)
5.0[b]	0.46 (30%)	0.61 (23%)	1.0 (14%)	36 (0.4%)
10[c]	0.61 (48%)	0.76 (38%)	1.2 (24%)	36 (0.8%)
50[d]	1.7 (82%)	1.9 (74%)	2.3 (61%)	37 (3.4%)
70[e]	2.3 (87%)	2.5 (80%)	2.9 (69%)	38 (5.3%)

Intake from each source (see Sections 5.1-5.3):

Water:	0.5 ug/l:	0.014 ug/kg/day
	5.0 ug/l:	0.14 ug/kg/day
	10 ug/l:	0.29 ug/kg/day
	50 ug/l:	1.4 ug/kg/day
	70 ug/l:	2.9 ug/kg/day
Air:	1.4 ug/m^3:	0.23 ug/kg/day
	2.3 ug/m^3:	0.38 ug/kg/day
	4.8 ug/m^3:	0.79 ug/kg/day
	220 ug/m^3:	36 ug/kg/day
Food:		0.09 ug/kg/day

[a] 11,430,000 individuals using public drinking water systems are estimated to be exposed to levels $\geq$ 0.5 ug/l (5.3% of population using public water supplies).

[b] 874,000 individuals using public drinking water systems are estimated to be exposed to levels > 5.0 ug/l (0.4% of population using public water supplies).

[c] 440,000 individuals using public drinking water systems are estimated to be exposed to levels > 10 ug/l (0.2% of population using public water supplies).

[d] 105,000 individuals using public drinking water systems are estimated to be exposed to levels > 50 ug/l (< 0.1% of population using public water supplies).

[e] No individuals using public drinking water systems are estimated to be exposed to levels > 70 ug/l.

Brodzinsky and Singh (1982) calculated a median urban/suburban air level of tetrachloroethylene of 2.3 ug/m^3 based on air monitoring data. Assuming an air level of 2.3 ug/m^3 and the estimated tetrachloroethylene intake of 0.09 ug/kg/day in foods, drinking water would be the predominant source of tetrachloroethylene exposure in the adult male at drinking water levels above 16 ug/l. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of tetrachloroethylene in drinking water and low concentrations of tetrachloroethylene in ambient air and food are unknown.

Population-dose estimates for tetrachloroethylene in drinking water and air were presented previously. Estimates for drinking water ranged from 0.36-3.4 x 10^8 ug/day x persons; the estimate for ambient air was 1.37 x 10^9 ug/day x persons. These estimates suggest that ambient air may be a greater source of exposure to tetrachloroethylene than drinking water on a general population basis. Comparison of these estimates, however, may be deceiving since the same population-dose level can occur if: 1) a whole population is exposed to moderate levels of a chemical or 2) some segments of the same population are exposed to high levels and others to low levels. The population-dose values presented give no indication of the relative predominance of drinking water and air as specific sources of tetrachloroethylene on a site-by-site or subpopulation basis.

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V. HEALTH EFFECTS IN ANIMALS

Acute exposure

Klaassen and Plaa (1966) found the intraperitoneal 24-hour LD_{50} in mice to be 2.9 ml/kg (4700 mg/kg). Lethal doses produced anesthesia and death within a few hours. Histological examination revealed enlargement of hepatocytes, cellular infiltration and vacuolation and slight necrosis in the liver. Minimal necrosis of the convoluted tubules and hydropic degeneration with increased phenolsulfonphthalein (PSP) clearance occurred in the kidney. These changes, which are of an inflammatory nature, were accompanied by trace accumulation of lipid and occurred only at near lethal doses.

Klaassen and Plaa (1966, 1967) estimated the ED_{50} for liver and kidney damage in dogs and mice. The ED_{50} values for organ dysfunction were measured by BSP, SGPT, glucose, protein and phenolsulfonphthalein. They also determined the potency ratio,(the ratio of the LD_{50} to the ED_{50}). SGPT elevation, and BSP or PSP excretion were used to determine liver and kidney function; respectively. The data are summarized in Table V-1.

When two groups of 10 mice were given either 4150 mg/kg or 8300 mg/kg intraperitoneally, there was still no significant kidney dysfunction as determined by lack of protein or glucose in urine (Plaa and Larson, 1965). The authors reported necrosis of the proximal convluted tubules in one of six mice given the smaller dose of tetrachloroethylene intraperitoneally

TABLE V-1

24-HR MEDIAN LETHAL AND EFFECT DOSES OF TETRACHLOROETHYLENE

Species	LD_{50} (mg/kg)	ED_{50} for clinical tests (mg/kg)		
		BSP Retention	SGPT	PSP Retention
Mouse	4700 i.p.	4700	4700	ND
Dog	4150 i.p.	ND	1200	2300

Note: ND = Not determined.

Source: Adapted from Klaassen and Plaa (1966; 1967)

and swelling of the tubules in four of six. Only one of the six demonstrated significant proteinuria afer 24 hours with the 4150 mg/kg dose, but two of four mice given the 8300 mg/kg dose of tetrachloroethylene had significant proteinuria. Tetrachloroethylene was judged, on the basis of prolongation of pentobarbital sleeping time, to have a very low hepatotoxicity compared to other chlorinated solvents (Plaa et al., 1958).

Gehring (1968) found the i.p. 24-hr LD_{50} in the mouse to be 5500 mg/kg, a value similar to that reported by Klaassen and Plaa (1966). The author stated that the ED_{50} for elevation of the serum glutamic-pyruvic transaminase level was 3900 mg/kg. In concurrent inhalation experiments in which mice were exposed to 3700 ppm for 9-12 hours continuously, Gehring showed that the duration of exposure needed to produce a significant elevation of SGPT (ET_{50}=470 min.) was much longer than that needed to produce anesthesia (ET_{50}=24 min.). In fact, no overlap occurred between the dose at which 99% of the animals would be anesthetized and only 1% of the animals would show significant elevation of SGPT. Therefore, elevation of SGPT and the accompanying liver dysfunction would be expected to occur in only a small number of the animals exposed via inhalation in acute, high level doses.

Mongrel dogs which were dosed with PCE intraperitoneally showed moderate liver toxicity (neutrophilic infiltration of portal and sinusoid areas) and an elevation of SGPT activity. Slight calcification of the kidney tubules was seen, with increased excretion of phenosulfonphthalein only at near lethal doses (Klaassen and Plaa, 1967). The LD_{50} for mongrel dogs was 2.1 l/kg (3400 mg/kg). Even though the LD_{50} was less than that for mice, less severe liver and kidney effects were seen in the dogs.

Rowe, et al. (1952) determined the mortality rate, gross response and organic injury from single inhalation exposures to tetrachloroethylene at 2,000 ppm over various exposure durations. The most characteristic effect in rats was depression of the central nervous system manifested by drunken behavior, stupor, unconsciousness and respiratory failure. Cardiac failure possibly occurred. Unconsciousness was not observed at 2,000 ppm, but occurred at 3,000 ppm within a few hours and at 6,000 ppm within a few minutes. Deaths occurred during or immediately after exposure. Those animals which survived exposures causing high mortality exhibited a slight transient whole body weight loss and liver damage characterized by minor increases in organ weight and total lipid content, with slight cloudy swelling.

Lazarew (1929), using 151 experimental animals, determined that the inhalation concentration of tetrachloroethylene able to cause unconsciousness was 2,211 ppm (15,000 mg/m^3). Complete narcosis with loss of reflexes occurred at 2,948 ppm (20,000 mg/m^3) and the minimal fatal concentration of the solvent was 5,896 ppm (40,000 mg/m^3). Exposure duration did not exceed two hours.

Fujii (1975) dosed male rabbits once with 2,158 mg PCE/kg by gavage and observed a 50% increase in the serum lipoprotein level 48 hours after exposure. This increase was still evident two weeks after treatment. Changes in serum enzyme activities (i.e. alkaline phosphatase, glutamate-oxalacetate transaminase, glutamate-pyruvate transaminase), indicative of liver damage, were mild and transient. Single intraperitoneal doses to rats of PCE, ranging from 50 to 330 mg/kg, however, increased serum glutamate oxalacetate transaminase activity from 20 to 440%, (Cornish, et al. 1973). Phenobarbital pretreatment did not alter the response.

Kylin, et al. (1963) noted moderate fatty infiltration of the liver of female albino mice with a single four-hour inhalation exposure to as little as 1,340 mg PCE m^3 (200 ppm). At 400 ppm, most animals showed moderate to massive infiltration. At 1600 ppm, very pronounced infiltration was observed, but there was no evidence of cell necrosis. At 3000 ppm, serum ornithine carbaminoyl transferase (S-OCT) was elevated occasionally, but not significantly. High S-OCT levels would be an indication of liver cell necrosis.

Ogata et al. (1968) reported a decrease in hepatic ATP levels with a proportional increase in total hepatic lipids and triglycerides in mice exposed to 800 ppm tetrachloroethylene for three hours. ATP levels dropped from 0.8 mg/g liver before exposure to slightly over 0.35 mg/g liver at the end of the exposure period. The levels continued to decrease slightly until eight hours after exposure, then started to recover by 20 hours, when they reached 0.4 mg/g. At the same time, total liver lipids increased from 2 mg/g body weight to about 3.5 mg/g at eight hours where they remained at 20 hours post-exposure. Triglyceride levels climbed from <10 mg/g liver before exposure to nearly 30 mg/g eight and 20 hours after termination of exposure.

Savolainen et al. (1977) reported "subtle" effects--no statistical analysis--on 10 Sprague-Dawley rats exposed to 200 ppm (1350 mg/m^3) tetrachloroethylene 6 hr/day for four days. Marked sequestration of the solvent occurred in fat and brain. The effects included an apparent diminishing of brain RNA content and an increase in non-specific cholinesterase activity on the 5th day and behavioral difference from controls (increased preening). No consistent effects were seen on brain protein content although brain glutathione content changed in parallel with the RNA. Liver levels of glutathione P-450 did not exhibit consistent change. The data suggest that the toxic effect of PCE can be observed in CNS changes earlier than in alterations of liver function, at least, following inhalation exposure.

Goldberg et al. (1964) reported that PCE caused an 80 percent loss of both avoidance and escape responses in female rats after a single 4-hour exposure to 15,600 mg/m^3 (2300 ppm). These effects were attributable primarily to an overt ataxia which disappeared during subsequent exposure periods (4 hours per day/5 days per week/2 weeks).

Tarasova (1975) found that following continuous inhalation exposure of rats to tetrachloroethylene (7 days at 185 ppm), there were morphological changes in mast cells characterized by increased vacuolization of the cytoplasm and conformational changes in the granules with some degranulization. Data by this and other authors suggest that the mast cells found in loose connective tissue respond easily to functional stress of tissue. The implications of this phenomenon are not fully understood at this time, but the response seems to be due to the toxic action of the chemical.

Tetrachloroethylene, as do a number of other low molecular weight chlorinated compounds, greatly increases bile duct-pancreatic fluid flow in rats (Hamada and Peterson, 1977). The resulting fluid has a markedly depressed protein content and a significantly altered ionic composition. The physiological significance of these observations has not yet been determined.

An industry study (Watanabe and Schumann, 1978; Schumann and Watanabe, 1979; Schumann, et al., 1980) reported an evaluation of tetrachloroethylene metabolism and hepatic binding in rats and mice following exposure to 10 or 600 ppm ^{14}C-tetrachloroethylene vapor for 6 hours, as well as to a single oral dose of 500 mg/kg in corn oil. The mouse metabolized 8.5 times more tetrachloroethylene per kilogram body weight than did the rat, when exposed at the 10 ppm dose, and 1.6 times following the oral dose. The authors hypothesized that the mechanism of tetrachloroethylene-induced carcinogenesis in mice is related to the greater extent of tissue macromolecular binding of the highly reactive intermediate epoxide in liver and the resulting injury, not to a genetic event.

Ogata and Kuroda (1962) injected tetrachloroethylene subcutaneously into mice (1.5 ml/kg, 10 or 20 injections given every other day). Increased beta globulin (24.4 to 30.3%) and reduced albumin (41.4 to 38.8%) were observed in the serum. No statistics were reported for these results, but cursory review of the data would suggest that the alteration in the albumin level probably was not significant.

Subacute/subchronic exposure

Rowe, et al. (1952) exposed eight female rats to 1600 ppm (10,900 mg/m^3) seven hours/day, five days/week for 18 exposures over a period of 25 days. During the first week, the animals were drowsy when removed from the exposure chamber. During the second week, the animals exhibited what was interpreted to be stimulation of the cholinergic nervous system, since the responses could be prevented by prior administration of atropine. The nervous responses included: marked salivation, restlessness as evidenced by continuous movement, a biting reflex when coming into contact with another animal in the chamber, a disturbance of coordination and equilibrium and a conspicuous "scratch reflex." At autopsy, the rats showed a decrease in body weight and hepatic and renal hypertrophy. Male guinea pigs receiving eight seven-hour, 1600 ppm exposures over 10 days lost weight and suffered hepatic hypertrophy accompanied by moderate fatty central degeneration and slight degeneration of the germinal epithelium of the testis.

Rats, rabbits and guinea pigs were subjected to repeated seven-hour exposures at 2500 ppm (17,000 mg/m^3) (Rowe, et al. 1952). The rats experienced rapid deaths. Only two survived 13 exposures over 18 days. Death was due to CNS depression. The only pathology present was in the liver, with slight to moderate swelling and a few small, widely dispersed fat vacuoles. The rabbits received 28 exposures over 39 days.

They suffered sufficient CNS depression to render them helpless, but not unconscious. Slight degeneration of the liver was noted. Guinea pigs responded in a manner similar to the rat during 18 exposures over 24 days. Besides a slight hepatic effect, there was also an increase in kidney weights with slight to moderate cloudy swelling of the tubular epithelium.

Female rats exposed to 400 ppm (2720 mg/m^3) during 14 seven-hour exposures over 18 days revealed no abnormalities as judged by general appearance and behavior, body and organ weights, several blood parameters testing for liver damage and tissue examination. In contrast, 15 male guinea pigs showed considerable depression of growth as well as increased liver and kidney weights from the same exposure protocol. Changes in growth and liver weight were also evident in guinea pigs exposed to 200 ppm (1360 mg/m^3) over the same time period. No evidence of severe adverse effects were observed in female guinea pigs exposed to 100 ppm (680 mg/m^3) during 13 seven-hour exposures over 17 days.

Exposure of mice to a concentration of 200 ppm (1360 mg/m^3) tetrachloroethylene 4 hours daily, 6 days a week for up to 8 weeks was found to increase the severity of the liver lesions caused by single exposures to the same dose (Kylin, et al. 1965). Morphological changes tended to progress over time, until at eight weeks, virtually 80% of the liver was characterized by massive infiltration of fat, usually central, involving at least half of the lobules. Liver fat content doubled during the first week of exposure, then showed no further increase.

Experiments by Mazza (1972) showed that liver mitochondrial damage resulted when rabbits were exposed to approximately 2,790 ppm tetrachloroethylene for 4 hr daily, 5 days/week, for 9 weeks (see Table V-2). Measurement of the activity of glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase and glutamic dehydrogenase, before and at 15, 30 and 45 days after initiation of the experiments, showed a significant increase for all enzymes by 45 days. Further tests demonstrated damage to cytoplasmic and mitochondrial structures of the liver parenchyma with the mitochondrial damage being greater. The animals presented no symptoms during exposure other than weight loss of 500-600 grams and reduced food intake.

Brancaccio et al. (1971) measured renal function in 12 male rabbits treated by inhalation of tetrachloroethylene at 2,200 ppm (15,000 mg/m^3) for 45 days, four hours/day, six days/week. By measuring creatinine and para-aminohippuric acid clearance, the authors concluded that the renal tubular function was more affected than the glomerular capacity by tetrachloroethylene exposure. Glomerular filtrate and renal plasma flow were reduced "at the level of statistical significance." However, no raw data or description of statistical methods are included in the publication. Maximum tubular excretion was diminished significantly.

Inhalation of tetrachloroethylene by mice at 15 or 75 ppm (100 or 500 mg/m^3), 5 hr/day for 3 months, decreased by 5-10% the electroconductance in the gastrocnemius muscle.

TABLE V-2

EFFECT OF INHALATION EXPOSURE OF RABBITS TO TETRACHLOROETHYLENE ON THE ACTIVITY OF LIVER ENZYMES

	GDH[a] (mU/ml)	GOT[a] (umol/ml)	GPT[a] (umol/ml)	Schmidt Index[a]
Before exposure[b]	0.10 ± 0.06[c]	0.37 ± 0.03	0.33 ± 0.03	6.70 ± 0.37
After 15 days	0.10 ± 0.05	0.38 ± 0.04	0.33 ± 0.03	6.72 ± 0.26
After 30 days	0.49 ± 0.05	0.49 ± 0.05	0.44 ± 0.03	1.92 ± 0.06
After 45 days	0.81 ± 0.07	0.74 ± 0.09	0.71 ± 0.10	1.79 ± 0.09

[a] GDH = Glutamic dehydrogenase.
GOT = Glutamic-oxaloacetic transaminase.
GPT = Glutamic-pyruvic transaminase.
Schmidt Index = GOT + GPT/GDH.

[b] Exposure was at 15 mg/liter (2790 ppm), 4 hours/day, 5 days/week, for 9 weeks.

[c] Mean ± S.D.; N = 15.

Source: Mazza (1972).

The contraction of the muscle also was reduced by 8, 12 and 24% at 1, 2 and 3 months, respectively. A month after the exposure was terminated, the muscle activity had returned to the pre-exposure level (Dmitrieva, 1968).

Mazza and Brancaccio (1971) investigated the possibility that tetrachloroethylene is stimulatory to the adrenals. They exposed 10 rabbits one hour/day, six days/week for 15 days to concentrations of 2,200 ppm (14,920 mg/m^3) tetrachloroethylene and measured gradually-increasing levels of both adrenocortical and adrenomedullary hormones. Urinary excretion of 3-methoxy-4-hydroxy mandelic acid (the principal catecholamine metabolite) also increased slightly during this time. None of these changes was statistically significant.

Longer-term exposure

Rats, guinea pigs, rabbits and monkeys were exposed to tetrachloroethylene via inhalation at 400 ppm (2720 mg/m^3) and guinea pigs at 100 ppm (680 mg/m^3) or 200 ppm (1360 mg/m^3) for periods up to 250 days (Rowe, et al., 1952). Each exposure period was for seven hours, five days per week. At 100 ppm, seven male and four female guinea pigs tolerated up to 132 exposures over 185 days, exhibiting only a slight increase in liver weight in the females and the appearance of a few fat granules in the central areas of the liver of two males and all of the females. At 200 ppm, eight males and eight females tolerated up to 158 exposures over 220 days without evidence of gross adverse effects. There was a significant decrease in growth rate and an increase in liver weight in the females. An increase in the total lipid and esterified cholesterol levels also were observed. Slight central fatty degeneration without cirrhosis also occurred.

No adverse effects were seen after exposure to 400 ppm (2720 mg/m^3) in rats receiving 130 exposures over 183 days, in rabbits receiving 159 exposures in 222 days or in monkeys receiving 179 exposures in 250 days. However, guinea pigs exposed 169 times over 236 days showed a decrease in growth rate, an increase in liver weight and an increase in neutral fat and esterified cholesterol in the liver. Moderate fatty degeneration and slight cirrhosis were evident in the liver.

Carpenter (1937) exposed rats of both sexes to 70 ppm (475 mg/m^3), 230 ppm (1560 mg/m^3) or 470 ppm (3200 mg/m^3) tetracloroethylene for 150 days or to 7,000 ppm (47,500 mg/m^3) for 50 days. Each exposure lasted eight hours per day, five days per week. Fertility among the females was either not affected or was slightly stimulated when compared with the control group. No alteration in blood calcium and glucose, icteric index or bilirubin was noted. Periodic white blood cell counts were always found to be within normal limits. There was no evidence of gross pathology upon autopsy of animals remaining free from infection. No histopathology was noted at the lowest dose. Some splenic congestion and swelling also occurred. At the 470 ppm dose, the liver was congested and exhibited cloudy swelling 46 days after termination of exposure. No evidence of fatty degeneration or necrosis was seen. The kidney showed increased secretion, cloudy swelling and desquamation; the spleen was congested and its pigment increased. In those animals exposed to 7,000 ppm for 50 days, the liver showed some congestion with marked cloudy and granular swelling but no fatty degeneration or necrosis. The kidney and spleen exhibited changes as reported above.

A longer-term inhalation study with a stabilized commercial tetrachloroethylene formulation (Dowper^R) demonstrated an increase in mortality from the 5th to the 24th month of the study in male, but not female, Sprague-Dawley rats exposed to 600 ppm (4068 mg/m^3) for 5 days/week, 6 hr/day for 12 months followed by up to 19 months' observation (Rampy et al., 1978). The mortality increase appeared to be associated with an earlier onset of "spontaneous advanced chronic renal disease" in the males only, according to this report. Other groups of animals were exposed to 0 or 300 ppm with the same regimen. The interim report (on 30 tissues from the exposed and control animals) described increased numbers of inflammatory cells in the kidneys and focal progressive nephrosis in the solvent-exposed rats of both sexes, especially at the high (600 ppm) inhalation dose. No statistically significant changes were noted in animals exposed to 300 ppm at the same time. Criteria examined were: body weights, mortality, hematology, urinalyses, clinical chemistry, cytogenetic data, terminal organ weights and gross and histological tissue changes, including tumor incidence.

Mean hematologic values were determined 6 days after the end of the 12-month exposure and one year after the conclusion of the 12-month exposure. The 6-day postexposure determinations of mean hemoglobin for female rats exposed at the 600 ppm level and mean white blood cell counts for females exposed at both concentrations were significantly lower than the respective values for the control females. However, when the determinations were repeated one week later, no statistically significant differences were found. The authors concluded that exposure to PCE did not result in an effect on hematologic parameters. Actually, the first evaluation of these parameters should have been done concurrently with termination of exposure. The 6-day delay may have allowed some return to normal, and thus, an effect may have been missed.

Navrotskii, et al. (1971) exposed rabbits via inhalation to 2, 10 or 100 mg/m^3 (0.3, 1.5 or 15 ppm, respectively) three to four hours per day for seven to eleven months. Parameters which the authors felt were very sensitive for detecting early adverse responses to low intensity exposures to toxic substances were tested. These parameters involving the immune system measured antibody titers in the indirect hemagglutination test and the phagocytic activity of the blood.

The results, as described by Navrotskii, et al. (1971), and translated from Russian, are very interesting in that they describe the induction of functional alterations in the body after very low levels of exposure to the chemicals under study (chlorinated ethanes and ethenes). For example, no change in the antibody titer was observed after exposure to 2 mg/m^3. At 10 mg/m^3, trichloroethylene had a more pronounced effect than tetrachloroethylene. However, neither the magnitude nor the direction of the changes was stated. At 100 mg/m^3, suppression of agglutinin production was observed within 1 to 1-1/2 months after initiation of exposure. Antibody titers were lowered, up to 2.5-7.5 times lower than control, after 8-9 months. However, the exact change induced by tetrachloroethylene was not stated. Tetrachloroethylene increased phagocytic activity at both 10 and 100 mg/m^3 during the first month, followed by a suppression by the third month (magnitude of change again not quantified).

In addition, up to 10 mg/m^3, tetrachloroethylene had no effect upon the acetycholine or acetylcholine esterase blood levels. No changes were seen in total protein and protein fraction levels. At 100 mg/m^3, increased globulins were observed, but total proteins did not change significantly. Only the 100 mg/m^3 exposure level caused noticeable histopathological changes in the parenchymal cells of the liver and kidney. The animals were sacrificed at some unstated time interval after cessation of exposure. In light of all these uncertainties and the fact that statistical analyses of the data were not conducted, caution should be exercised when interpreting these results.

Additional studies of the effects on the immune system of tetrachloroethylene-exposed experimental animals have been reported. Chinchillas, exposed at 1.5 or 15 ppm (10 or 100 mg/m^3) by inhalation 3 hr/day, 6 days/week, for 8 to 10 months, exhibited significant changes in antibody production to a Salmonella typhosa antigen challenge. At 1.5 ppm, only the 7-S antibody profile and the 7-S globulins were changed (Shmuter, 1972).

The National Cancer Institute (NCI) carcinogenesis bioassay of tetrachloroethylene revealed a high incidence of toxic nephropathy in both male and female B6C3F1 mice exposed orally to 536 and 386 mg PCE/kg, respectively, 5 days a week for 78 weeks (NCI, 1977). Similar results were obtained in both male and female Osborne-Mendel rats exposed to 471 and 474 mg PCE/kg, respectively, over the same treatment course.

Dmitrieva and Kuleshov (1971) reported aberrancies in the EEG in rats exposed for 5 months to 15 ppm tetrachloroethylene. Histologic examination of their brains showed swelling of some cerebral cortical cells with isolated cells containing vacuoles in the protoplasm. Electrical conductivity and cerebral tissue impedance changes that were seen in the exposed animals apparently returned to normal 1 month after cessation of exposure; only the EEG pattern remained different. The toxicological effects of tetrachloroethylene are summarized in Table V-3.

Teratology

Schwetz et al. (1975) assayed for reproductive and teratogenic effects in Sprague-Dawley rats and Swiss Webster mice exposed to 300 ppm tetrachloroethylene by inhalation for 7 hr/day from gestation day 6 to gestation day 15. Caesarian sections were done on day 21 (rats) and day 18 (mice). The authors reported a small but statistically significant reduction in the body weights of exposed pregnant rats (4-5%), but not exposed pregnant mice. Pregnant mice did, however, exhibit a significant increase in the mean relative liver weights and their fetuses weighed significantly less than the controls. In the reproductive performance subgroup, the number of resorptions per implantation site was over two times the control level in exposed dams (rats), and the average fetal body weight in exposed groups was below control values (mice), both significant at the 0.05 level. In the mouse pups, significant subcutaneous edema, delayed skull ossification and the presence of split sternebrae were seen following maternal tetrachloroethylene exposure as described above. No other anomalies were seen in controls.

TABLE V-3

SUMMARY OF TOXICOLOGICAL EFFECTS OF TETRACHLOROETHYLENE ON ANIMALS

Animal	Route	Dose	Length of exposure: effects	Reference
Mouse	Oral	4-5 ml/kg (6492-8115 mg/kg)	Death in 2-9 hr from central nervous system depression	Lamson et al. (1929)
Rabbit	Oral in oil	5 ml/kg (8115 mg/kg)	Death in 17-24 hr	Lamson et al. (1929)
Cat	Oral in oil	4 ml/kg (6492 mg/kg)	Death within hours	Lamson et al. (1929)
Dog	Oral in oil	4-25 ml/kg (6492-40575 mg/kg)	Death in 5-48 hr	Lamson et al. (1929)
Cat	Oral in milk or water	0.5 ml/kg (812 mg/kg)	No effect	Maplestone and Chopra (1933)
Cat	Oral in milk or water	1.0 ml/kg (1623 mg/kg)	Drowsiness and unsteadiness of hind legs, recovery in 3 days	Maplestone and Chopra (1933)
Cat	Oral in milk or water	4.5 ml/kg (7304 mg/kg)	More severe symptoms	Maplestone and Chopra (1933)
Cat	Oral in milk or water	5 ml/kg (8115 mg/kg)	Death in 24 hr	Maplestone and Chopra (1933)
Rabbit	Oral	5 ml/kg (8115 mg/kg)	1 dose:death within 24 hr	Von Oettingen (1937)
Cat	Oral	4 ml/kg (6492 mg/kg)	Death in 36 hr	Von Oettingen (1937)
Mouse	Oral in oil	4-5 ml/kg (6492-8115 mg/kg)	LD_{50}	Kohne (1940)

TABLE V-3 (Continued)

Animal	Route	Dose	Length of exposure: effects	Reference
Mouse	Oral	6 ml/kg in oil (9738 mg/kg)	LD_{100}	Kohne (1940)
Mouse	Oral	0.109 ml ± 0.011 ml (8845 mg/kg)	LD_{50} for mice 19-23 g	Dybing and Dybing (1946)
Mouse	Oral	0.134 ml (in oil) ± 0.011 ml (10,874 mg/kg)	LD_{50} for mice 19-23 g	Dybing and Dybing (1951)
Mouse	Oral	5.0 ml/kg (8115 mg/kg)	1 dose:50% death in 24 hr	Wenzel and Gibson (1951)
Rat	Oral	13 g/kg	1 dose: LD_{50}	Smyth, et al (1969)
Flatfish	Dissolved in water	737 ppm (5000 mg/m^3)	Lethal to 50% of fish in 96 hr	McConnell et al. (1975)
Mouse	Inhalation	40,000 mg/m^3 (5,900 ppm)	Minimal fatal concentration	Lamson et al. (1929)
Dog	Inhalation	9,900 ppm (68,000mg/m^3)	Narcosis, marked salivation, narrow margin of safety	Lamson et al. (1929)
Mouse	Inhalation	20,000 mg/m^3 (2,950 ppm)	Minimal narcotic effect	Lazarew (1929)
Mouse	Inhalation	16,000 mg/m^3 (2,400 ppm)	Disturbed equilibrium in 64 min and rest in 134 min but no narcosis in	Crescitelli (1933)

TABLE V-3 (Continued)

Animal	Route	Dose	Length of exposure: effects	Reference
Mouse	Inhalation	17 mg/l (2,500 ppm)	Disturbed equilibrium in 42 min and rest in 67 min but no narcosis in 120 min	Crescitelli (1933)
Mouse	Inhalation	18 mg/l (2,600 ppm)	Disturbed equilibrium in 17 min and rest in 30 min, narcosis occurred in 47 min and recovery within 150 after exposure terminated	Crescitelli (1933)
Mouse	Inhalation	23 mg/l (3,400 ppm)	Disturbed equilibrium in 11 min and rest in 33 min, narcosis occurred in 54 min, and death of one-third of the animals within 190 min after exposure	Crescitelli (1933)
Mouse	Inhalation	25 mg/l (3,700 ppm)	Disturbed equilibrium in 12 min and rest in 21 min, narcosis occurred in 31 min and death of two-thirds of the animals within 164 min after exposure	Crescitelli (1933)
Mouse	Inhalation	40 mg/l (5,900 ppm)	Disturbed equilibrium in 4 min and rest in 8 min, narcosis occurred in 14 min and death of all animals by 49 min after exposure	Crescitelli (1933)
Rat	Inhalation	230 ppm	8 hr/day, 5 days/week, 7 months: congestion and sparse granular swelling of kidneys	Carpenter (1937)

TABLE V-3 (Continued)

Animal	Route	Dose	Length of exposure: effects	Reference
Rat	Inhalation	470 ppm	8 hr/day, 5 days/week, 7 months: increased secretion, cloudy swelling and desquamation of kidneys, congestion and cloudy swelling of liver; congestion of spleen	Carpenter (1937)
Rat (Sherman)	Inhalation	4,000 ppm (27,000 mg/m^3)	4 hr: LD_{50}	Carpenter et al. (1949)
Mouse	Inhalation	5,218 ppm	24 hr:50% death	Friberg et al. (1953)
Rat	Inhalation	1,600 ppm	18 7-hr exposures: drowsiness, stupor, increased salivation, extreme restlessness, disturbance of equilibrium and coordination, biting and scratching reflex	Rowe et al. (1952)
Rat	Inhalation	2,500 ppm	1-13 7 hr exposures:loss of consciousness and death	Rowe et al. (1952)
Rat	Inhalation	3,000-6,000 ppm	Up to 8 hr: Increase in liver weight, increase in total lipid content of liver accompanied by a few diffusely distributed fat globules	Rowe et al. (1952)

TABLE V-3 (Continued)

Animal	Route	Dose	Length of exposure:effects	Reference
Rabbit	Inhalation	2,500 ppm	28 7-hr exposures: central nervous system depression without unconsciousness	Rowe et al. (1952)
Guinea Pig	Inhalation	2,500 ppm	18 7-hr exposures: loss of equilibrium, coordination and strength	Rowe et al. (1952)
Guinea pig	Inhalation	100 ppm	137 7-hr exposures: slight increase in liver weight, in lipid content and several small fat vacuoles in liver	Rowe et al. (1952)
Mouse	Inhalation	400 ppm	169 7-hr exposures: increase in liver weight, increase in neutral fat and esterified cholesterol in the liver and moderate central fatty degeneration with slight cirrhosis	Rowe et al. (1952)
Mouse	Inhalation	200-1,600 ppm	8 hr/day, 3 days: increase in mortality and inhibition of growth	Schumacher et al. (1952)
Mouse	Inhalation	3,700 ppm	730 min: 50% death in 24 hr	Gehring (1968)
Mouse	Inhalation	3,700 ppm	24 min: anesthetization	Gehring (1968)
Mouse	Inhalation	3,700 ppm	470 min: liver dysfunction	Gehring (1968)

TABLE V-3 (Continued)

Animal	Route	Dose	Length of exposure:effects	Reference
Mouse	Inhalation	200 ppm	4 hr/day, 6 days/week, 1-8 weeks: fatty degeneration of the liver	Kylin et al. (1965)
Mouse	Inhalation	15-74 ppm	5 hr/day, 3 months: decreased electroconductance of muscle and amplitude of muscular contraction	Dmetrieva (1968)
Rabbit	Inhalation	2,211 ppm	45 days:significant reduction of glomerular filtration rate and the renal plasma flow; decrease of highest excretory tubular capacity (kidney damage)	Brancaccio et al. (1971)
Rabbit	Inhalation	2,211 ppm	45 days: increased plasma levels of adrenal cortical and adrenal medullar hormones; increased excretion of principal catecholamine metabolite	Mazza and Brancaccio (1971)
Rabbit	Inhalation	2,212 ppm	45 days: liver damage indicated by elevated SGPT, SGOT, SGLDH; marked reduction of Schmidt index	Mazza (1972)
Rat	Inhalation	44.2 ppm	Entire gestation period: decreased levels of DNA and total nucleic acids in the liver, brain, ovaries, and placenta	Ananina (1972)

TABLE V-3 (Continued)

Animal	Route	Dose	Length of exposure:effects	References
Mouse	Inhalation	300 ppm	7 hr/day, days 6-15 of gestation: increased liver weight; decreased fetal body weight; increased subcutaneous edema (fetal toxicity); minor skeletal abnormalities	Moolenaar (unpublished) (1975)
Rat	Inhalation	300 ppm	7 hr/day, days 6-15 of gestation: decreased maternal weight gain; increased incidence of fetal resorption	Moolenaar (1975)
Rabbit	Inhalation	15 ppm	3-4 hr daily, 7-11 months: moderately increased urinary urobilinogen; pathomorphological changes in the parenchyma of liver and kidneys	Navrotskii et al. (1971)
Rabbit	Inhalation	15 ppm	3-4 hr/day, 7-11 months: depressed agglutinin formation	Mazza (1972)
Rat	Inhalation	600 ppm	6 hr/day, 5 days/week, 12 months: increased mortality over controls	Leong et al. (1975)
Mouse	Intraperitoneal	2.9 ml/kg (4700 mg/kg)	1 dose: 50% death in 24 hr; liver dysfunction: hepatocytomegaly with cellular infiltration and vacuolization; slight necrosis only in lethal range; kidney dysfunction	Klaassen and Plaa (1966)

TABLE V-3 (Continued)

Animal	Route	Dose	Length of exposure:effects	Reference
Mouse	Intraperitoneal	3.4 ml/kg (5500 mg/kg)	1 dose:24 h-LD_{50}; liver dysfunction; enlargement of hepatocytes; vacuolization; slight necrosis	Gehring (1968)
Dog	Intraperitoneal	2.1 ml/kg (3400mg/kg)	Lethal to 50% of animals in 24 hr	Klaassen and Plaa (1967)
Dog	Intraperitoneal	1.23 ml/kg	Liver dysfunction (as measured by increased SGPT levels in 50% of animals) in 24 hr	Klaassen and Plaa (1967)
Dog	Intraperitoneal	2.32 ml/kg	Kidney dysfunction (as measured by increased retention of PSP in 50% of animals) in 24 hr	Klaassen and Plaa (1967)
Rabbit	Subcutaneous in oil	2.2 g/kg	Death in 24 hr	Barsoum and Saad (1934)
Mouse	Subcutaneous injection	1.5 ml/kg	Alternate days for 20-40 days: decreased serum albumin level, increased globulin levels	Ogata and Kuroda (1962)
Dog	Intravenous	85 mg/kg	Death in 30 min	Barsoum and Saad (1934)

Effects on fertility were studied by Carpenter (1937), exposing rats to 70, 230 or 470 ppm tetrachloroethylene for 8 hr/day, 5 days/week for 28 weeks. The number of litters conceived was analyzed by an index value defined as the actual number of litters divided by the possible number of litters. Carpenter's data indicated that the solvent stimulated reproductive performance, especially at higher doses.

Shumacher et al. (1962) exposed 3 week-old mice for 8 hr/day, 3 days each in succession, to 200, 400, 800 and then 1,600 ppm tetrachloroethylene. The exposure produced significant mortality and growth inhibition in survivors.

Female Long-Evans hooded rats were exposed to a time-weighted average of 1000 ± 125 ppm tetrachloroethylene via inhalation to determine whether exposure before mating and during pregnancy was more detrimental to the embryo than exposure during gestation alone (Tepe, et al., unpublished manuscript). Animals were randomly assigned to one of four treatment groups containing 30 animals each. The groups were as follows:

A---tetrachloroethylene exposure before mating and during pregnancy

B---tetrachloroethylene exposure before mating, filtered air during pregnancy

C---filtered air before mating, tetrachloroethylene during pregnancy

D---filtered air only before mating and during gestation

Premating exposures were conducted for 6 hr/day, 5 days/week for two weeks, after which two females were placed in a cage overnight with a breeder male. Exposure continued until pregnancy was confirmed by the presence of sperm in a vaginal smear. This was considered to be Day 1 of gestation. At that time, the exposure pattern was changed to 6 hr/day, 7 days/weeks through Day 20 of gestation. Half of each treatment group was sacrificed on Day 21.

Maternal body weights were taken every four days including Days 1 and 21. The average body weights on Day 1 for each group indicate that Group A weighed slightly less than the other groups at that time. Percent weight gains throughout gestation were the same in all groups except for Group B in which they were elevated. Dams exposed to tetrachloroethylene during gestation (Groups A and C) had significantly elevated relative liver weights.

Ethoxycoumarin dealkylase and ethoxyresorufin dealkylase, indicative of cytochrome P-450 and P-448 activities, respectively, were measured on both maternal and fetal livers. Maternal ethoxycoumarin dealkylase activity was elevated significantly with exposure during gestation in Groups A and C when compared with Groups B and D. No parallel elevation was noted in the fetal liver within these groups. Ethoxyresorufin dealkylase activity was not significantly altered in maternal liver, and was not detectable in fetal livers.

With respect to measurements of embryotoxicity, dams in Group C had slightly depressed number of corpora lutea, implantation sites, live fetuses and ratio of live fetuses to implantation sites. These changes were not significant by two-way analysis of difference or when one-way analysis was applied in comparison with Group D. These were no statistically significant treatment-related effects in the numbers of resorptions or their distribution in litters or in the sex ratio. The most significant effect was a depression of fetal body weight in Groups A and C, i.e. those groups exposed to PCE during pregnancy.

The authors claimed that no major skeletal malformations were observed among the fetuses evaluated. The most frequently-observed anomalies observed were delayed ossification of the sternum and missing 26th or 27th vertebrae. When total anomalies were summed, Group A was found to be significantly elevated over Groups B and D. Although the total number of anomalies in Group C was elevated, the change was not statistically significant. Nevertheless, taking the results as a whole, it was shown that exposure to 1000 ppm tetrachloroethylene before mating and during pregnancy results in a elevation of variation-from-normal skeletal anomalies relative to exposure before mating alone or during pregnancy alone, or to filtered air.

Anomalies in the soft tissues were also noted, particularly kidney dysplasia and misplaced right ovaries in females. The latter was considered by the authors to be a strain-related anomaly. The kidney dysplasia was considered to be treatment-related since it was found only in litters from dams exposed during pregnancy. The total number of soft tissue anomalies was elevated significantly only in Group C when compared with the controls.

Nelson, et al. (1979) conducted a behavioral teratology study in which they evaluated for possible functional effects in offspring of female rats exposed during gestation. When exposed to 900 ppm PCE by inhalation for 7 hours/day on Days 7-13 or 14-20 of gestation, pregnant Sprague-Dawley rats ate less feed and gained less weight than did the controls. Pups from dams exposed on days 7-13 performed significantly less well on two tests of neuromuscular ability on certain days (the ascent and the rotorod tests). Pups whose mothers were exposed on days 14-20 of gestation performed more poorly in the ascent test than controls on one day, but better than controls at a later stage on the rotorod test. They also became relatively more active in the open field test.

Offspring of rats exposed on Days 14-20 to 100 ppm PCE for 7 hours showed no significant differences from control animals. This result is significant in that 100 ppm is the current OSHA permissible exposure limit, but higher than the ACGIH recommended TLV of 50 ppm.

Manson, et al. (unpublished manuscript) evaluated the the postnatal development of offspring exposed prenatally to tetrachloroethylene. The conditions of exposure were those described above in the Tepe, et al. study. Half of each treatment group of pregnant rats was allowed to deliver and nurse its offspring to weaning. The purpose of the postnatal evaluation was to determine if the depression in body weight or the excess skeletal and soft tissue variants observed in the term fetuses from the teratology study persisted, and if the chemical possessed transplacental carcinogenic activity or neurobehavioral toxicity.

At four days after birth, litters were randomly culled to eight with equal representation of sexes when possible. At weaning, the litters were culled again, this time to four, two males and two females, with each being housed in individual cages.

The neurobehavioral testing concentrated on the evaluation of cognitive and motor abilities. The tests applied consisted of open field activity measurements at 10 and 20 days of age, running wheel activity measurements from 40-100 days of age and a visual discrimination test at 130-170 days of age. No significant differences were observed when compared with control groups for any of the tests conducted.

Mean body weights over the 18-month period were monitored. Offspring were weighed as a litter at Days 10 and 20, with analysis being separate for male and female offspring for periods up to 170 days of age. Male offspring in Groups A and C had significantly depressed weight gains from Days 30 to 170 of age. No significant differences were observed in the females over this time period, or in animals of both sexes at ages of 170-540 days.

Following completion of the visual discrimination testing on Day 170, one male and one female from each litter was sacrificed and subjected to gross necropsy. Minor lesions were present in the adrenal, spleen, lungs and GI tract. In the kidneys, however, hydronephrosis was observed more frequently in animals in treated groups than those in the control groups. This increase was not statistically significant when analyzed by Kruskal-Wallis analysis of variance.

The remaining animals in all groups were sacrificed at 18 months of age and grossly necropsied. The authors stated that none of the observed lesions could be definitively linked to treatment. They considered the observed changes to be reflective of aging, even though a preponderance of these lesions was observed in the brain, pituitary, spleen and male and female reproductive tracts of offspring in Group A. The authors felt that none of the lesions occurred with sufficient magnitude to indicate a clear treatment-related effect. In addition, they stated that the majority of lesions observed were not sufficiently indicative of neoplastic growth to warrant suspicion of transplacental carcinogenesis. It is difficult to evaluate these results because so few animals remained in each group from which the findings were made.

The section on teratogenicity, as it is now written, contains those studies considered to be pertinent to the development of a drinking water criteria document. Those studies that have been included have been reviewed for adequacy of the experimental design and for usefulness of the results in assessing the compound's teratogenic potential. Other studies which may be of interest to the reader include:

> Elovaara, E., K. Hemminki and E. Vainio. 1979. Effects of methylene chloride, trichloroethylene, tetrachloroethylene and toluene on the development of chick embryos. Toxicol. 12:111-119.

> Beliles, R.P., D.J. Brusick and F.J. Mecler. 1980. Teratogenic-mutagenic risk of workplace contaminants: trichloroethylene, perchloroethylene, and carbon disulfide. USDHEW, Contract No. 210-77-0047.

Stabilizer Toxicity

N-Methyl pyrrole, epichlorohydrin, epibromohydrin, amines such as allyl amine or methylmorpholine, and allyl glycidol ether have been used as stabilizers of tetrachloroethylene in various combinations. A comparison of the rodent LD_{50} levels for these additives to the LD_{50} level for tetrachloroethylene shows that most of the stabilizers are more toxic than tetrachloroethylene. The exception, N-methyl pyrrole, is less toxic; it takes a dose 9.3 times larger than a tetrachloroethylene dose to kill the same number of mice (Sax 1975; NIOSH, 1975). The other known stabilizers are much more toxic. Epichlorohydrin and epibromohydrin are 63 and 57 times more toxic than tetrachloroethylene, respectively. Allyl amine is 53 times more toxic and allyl glycidol ether is 15 times more toxic. The patent literature and communications from industry indicate that these stabilizer packages are constantly changing.

Tetrachloroethylene is usually stabilized by N-methyl pyrrole as an antioxidant. The other compounds on the list are added according to different formulations to inhibit the reactions which occur if some oxidation does take place. Epichlorohydrin and epibromohydrin are skin irritants and sensitizers. Epichlorohydrin has recently been implicated as a suspect carcinogen. An industrial epidemiology study found a higher-than expected rate of respiratory cancer deaths in workers previously exposed to epichlorohydrin. Another industry report suggested that epichlorohydrin workers had twice as many chromosomal aberrations as did controls. It is possible that this stabilizer has greater potential for inducing detrimental health effects than does tetrachloroethylene. The allyl glycidol ethers have been associated with radiomimetic effects, presumably reflecting biological alkylation (Kotin and Falk, 1963). The amines are basic and can produce chemical burns of the skin. Some sensitive individuals show hypersensitivity dermatitis and asthma-like reactions from exposure to the pure compounds, but their presence in small amounts as stabilizers probably does not present this hazard.

An unpublished report (Margard, 1978) on the mutagenicity of several trial stabilizer formulations was obtained. Since the data involved proprietary information, sufficient information to interpret the studies was unavailable. The bacterial assays (Ames tests) appeared to be well done, however. The document recognized (p. 25) that a broader assay profile (e.g., tests in addition to the Ames) would be desirable to demonstrate mutagencity or the lack of it. Tetrachloroethylene and stabilizers, however, reacted with the plastic in the sterile labware used to perform the tests. The mammalian cell cultures were many times more responsive to toxicity than were the bacterial cell systems. The data from the study suggest that tetrachloroethylene without stabilizers is nonmutagenic in the five Salmonella tester strains. However, the stabilized compound does appear to have mutagenic properties.

Summary

The most characteristic effect of acute exposure to tetrachloroethylene is on the central nervous system. It is manifest, at increasing concentrations, as depression, ataxia, unconsciousness, respiratory and, perhaps, cardiac arrest, and death.

As the dose increases, fatty infiltration of the central areas of the liver and, then, necrosis occur. Renal damage is seen usually at doses above which initial liver damage occurs. An elevation of total hepatic lipids has been reported. Liver triglycerides have also been shown to increase, concomitant with a decrease in hepatic ATP.

Additional changes that occur upon acute exposure include morphological changes in mast cells indicating a stress response, alterations in serum protein ratios, increased bile duct-pancreatic flow (a phenomenon of as yet unexplained significance), diminution of brain RNA content and an increase in brain non-specific cholinesterase activity accompanied by sequestration of tetrachloroethylene in body fat and brain tissue, and behavioral changes due principally to the loss of voluntary motor coordination.

Short-term/subchronic exposure effects are manifest principally as damage to the liver and kidney. Liver morphology progresses from congestion and cloudy swelling to fatty degeneration and necrosis. Kidney changes progress from an increase in weight and cloudy swelling of the tubular epithelium to desquamation and necrosis.

Other observed effects include possible stimulation of the adrenals, aberrancies in the EEG indicating subtle CNS effects, decrease in electroconductance and contraction of voluntary muscle, degeneration of the germinal epithelium of the testis, congestion of the spleen and depression of growth.

Longer-term exposure has been reported to result principally in the previously-described hepatic and renal damage. Body weight gain can be thwarted. In addition, it has been suggested that the chronic low exposure levels may affect the immune system in such a way as to reduce antibody titers and increase phagocytic activity. Unconfirmed evidence of anemia in a population of female rats and a possible leukopenia have been suggested. Again, subtle CNS effects have been reported, both physiological and morphological.

VI. HEALTH EFFECTS IN HUMANS

The information in this section is presented in the order of increasing duration of exposure.

Acute exposure

Experimental studies

As will be pointed out in the following paragraphs, the most characteristic response of an acute exposure to tetrachloroethylene is depression of the central nervous system. Unlike other chlorinated hydrocarbon solvents, there seems to be little potential for cardiac sensitization to epinephrine by tetrachloroethylene. With exposure at toxic levels, liver effects are diagnosed by changes in enzyme profiles. Chemical burns can occur with skin contact. There also can be local (as opposed to target organ) eye and respiratory tract irritation following airborne exposure to tetrachloroethylene (Stewart et al., 1961a).

Carpenter (1937), exposed four adult males to concentrations of industrial grade PCE averaging 3,200 and 6,300 mg/m^3 (472 and 911 ppm) for 130 and 95 minutes, respectively. At the low concentration, increased irritation of eyes and secretion by mucous membranes, sensory changes and a slight feeling of elation were observed. However, at the higher concentration, more definite signs of central nervous system depression were observed, i.e., lassitude, mental fogginess and exhilaration.

After 95 minutes, the 6,300 mg/m^3 concentration was raised to 10,000 mg/m^3 and signs of inebriation were observed. At 13,400 mg/m^3, all were forced to leave the chamber within 7.5 minutes because of faintness. The subjects also reported ringing in the ears at this concentration.

Rowe et al. (1952) studied the effects of single inhalation exposures to tetrachloroethylene on humans. The effects seen and doses which produced them are listed below in Table VI-1. Exposure to concentrations less than 100 ppm generally did not result in any disturbances.

Table VI-1

SUMMARY OF EFFECTS OBSERVED IN
HUMAN VOLUNTEER STUDY
(Rowe, et al., 1952)

Exposure Concentration	Effects
106 ppm Range: 83-130 ppm	Concentration was reported to be unobjectionable; odor was immediately apparent to individuals; one out of six people experienced congestion of frontal sinuses; transient eye irritation.
216 ppm Range: 206-235 ppm	Duration of exposure varied from 45 minutes to 2 hours. Odor was immediately apparent but acclimation readily occurred; eye irritation developed in 20 to 30 minutes and persisted; congestion of frontal sinuses and nasal discharge noted; slight dizziness and sleepiness noted by some individuals.

TABLE VI-1(Continued)

Exposure Concentration	Effects
280 ppm Range: 206-356 ppm	Duration of exposure up to two hours. General dislike of exposure; light-headeness; burning sensation in eyes; congestion of the frontal sinuses; "thick tongue" and tight mouth; transient nausea in some individuals, impaired motor coordination such that mental effort was required; recovery generally within one hour
600 ppm Range: 513-690 ppm	General dislike of exposure (10 min); eye and nasal irritation; dizziness; tightness and numbness of mouth; loss of inhibitions; motor coordination only with mental effort; recovery complete in one hour.
1060 ppm Range: 930-1185 ppm	Markedly irritating to eyes and upper respiratory tract; three of four subjects found this exposure intolerable after one minute and left chamber; the fourth subject experienced considerable dizziness following exposure for 2 minutes; recovery rapid.

Stewart, et al. (1961b) noted impaired ability to maintain a normal Romberg test, a measure of reflex coordination, in volunteer subjected to 1,300 mg/m^3 (190 ppm) after more than

30 minutes.

In a later study, Stewart et al. (1970) conducted a series of five experimental exposures at 100 ppm for seven hours each on consecutive days to simulate a workweek. Odor perception decreased over time during the course of the week. Perception at the beginning of each day decreased faster as the week progressed. After three hours' exposure on the first day, 3 of 8 subjects were unable to respond normally to a modified Romberg test, but were able to overcome this inability with greater mental effort. Subjective complaints during the five days included mild eye, nose and throat irritation, lightheadedness, mild frontal headache, sleepiness and some difficulty in speaking. These complaints decreased over the course of the study week. It should be noted that these subjects were confined to an exposure chamber and were not performing tasks as they would have been in a normal industrial setting. The Crawford and Flanagan behavioral tests, other neurological tests, pulmonary function tests and blood chemistries all remained normal throughout the week's experiments.

Stewart et al. (1974) exposed 19 volunteers to varying concentrations (20 to 150 ppm) of tetrachloroethylene for a 5-week period. EEG analysis and behavioral tests were run.

A single behavioral measure showed a change related to exposure level: the Flanagan coordination test registered lower scores on males exposed to 150 ppm for 7-1/2 hr/day, 5 days/week. Most subjects showed increased delta wave activity on the EEG after a 7-1/2 hr exposure to 100 ppm, but not to 20 ppm. The delta wave is part of the normal sleeping EEG.

This experiment is another indication of the slow elimination of tetrachloroethylene from the body. With repeated daily exposure, tetrachloroethylene builds up in the blood and tissues, especially in lipids (Stewart et al.,1974; Guberan and Fernandez, 1974).

Hake and Stewart (1977) exposed 12 subjects to 25 to 100 ppm tetrachloroethylene for 16.5 hr/week and measured central nervous system effects. One of the subjects was particularly susceptible to the solvent with a high level of subjective complaints, exposure-related EEG signs and behavioral test results. Breath analysis appeared to show no greater solvent absorption in this subject, and hypersensitivity to tetrachloroethylene (even allergy) was suggested.

In summary, the accumulated data indicate that there was minimal motor coordination effect at 100 ppm; light-headness and dizziness began to appear at 200 ppm; sensory change and slight inebriation appeared at 475 ppm. Between 1,000 and 1,500 ppm, acute central nervous system effects were noted immediately upon exposure. These are narcotic or anesthetic effects, which appear to be reversible on cessation of exposure.

Accidental Exposures

A case report (Stewart et al., 1961a) involved a workman exposed to a mixture of 50% tetrachloroethylene and 50% Stoddard solvent for 3.5 hours; this exposure produced unconsciousness. On the ninth postexposure day, liver function impairment was noted with urinary urobilinogen and serum bilirubin elevation; alkaline phosphatase became elevated slightly by two weeks and SGPT was elevated minimally on the 18th day after exposure. The authors simulated the exposure conditions and estimated the concentration of tetrachloroethylene to range from 25 to 1,470 ppm, averaging about 400 ppm.

Nine firemen responding to a leak of tetrachloroethylene at a dry-cleaning establishment were exposed to high levels of fumes for approximately three minutes. PCE was pouring from an open drain pipe into an open container in an enclosed basement area. All nine men became lightheaded and uncoordinated; each reported a sensation "as though they wanted to reach out and touch an object but somehow could not reach it." All of these are symptoms of a CNS effect. Exposure produced liver function changes as many as 63 days later. No neurological or behavioral follow-up was made, and there was no subject report of any nervous system problems beyond acute exposure (Saland, 1967).

Stewart (1969) reported that persons exposed to the solvent had a characteristic chloroform odor on their breath, and exhibited subclinical hepatitis, as indicated by an increase in urinary urobilinogen levels 7 to 10 days after exposure. Subjects recovered completely if organ damage due to anoxia (resulting from central nervous system depression) was avoided.

Stewart also reported the case of an individual accidentally acutely exposed to an anesthetic dose of PCE who exhibited a transient increase in serum glutamate-oxalacetate transaminase activity and a delayed elevation of urinary urobilinogen, both indicative of hepatic injury.

Patel et al. (1973) reported survival from another industrial exposure to tetrachloroethylene at an unknown concentration level in which a worker lost consciousness and lay for seven hours with whole-body exposure to the solvent. Acute pulmonary edema, coma, and hypotension with a blood pressure of 88/20 mm Hg followed, although kidney and liver function were reported to be normal.

Patel et al. (1977) reported a case of overexposure to tetrachloroethylene. The patient was so depressed on hospital entry that reflexes were absent and mechanical ventilation was necessary. Cardiovascular signs were normal throughout. Liver and kidney function tests were normal during the 4-day hospitalization and remained normal when tested "several weeks" after discharge.

Unconsciousness due to overexposure occurred in two cases reviewed by Hake and Stewart (1977), and, in both cases reversibility of all narcotic symptoms occurred. One exposure involved a patient on a respirator who was anesthetized when a workman washed the hospital respiratory air vent with tetrachloroethylene. The clinical condition did not otherwise change; temporary anesthesia was the only toxicity.

A dry cleaning operator also became unconscious and lay in a pool of tetrachloroethylene for 12 hours. He underwent a mild seizure and exhibited some temporary renal and liver toxicity. After 21 days, the CNS, liver and kidney tests were negative but the breath analysis continued to show tetrachloroethylene on Day 25.

There have been several reports of dermal response to tetrachloroethylene contact in occupational situations. These chemical burns vary in severity. Foot et al. (1943) described skin irritation resulting from the vapors contacting the skin under a respiratory mask. Ling and Lindsay (1971), described a case of extensive erythema and burn blisters (first and second degree solvent burns) on a laundry worker who, after being overcome by tetrachloroethylene fumes, fell and lay for 5 hours in the liquid solvent which had accumulated on the floor. Consciousness returned in 24 hours.

Munzer and Heder (1972) reported a case of eczema as a direct effect of exposure to tetrachloroethylene by a man in a dry cleaning plant. Erythema, not necessarily allergic, but possibly this type of reaction, has also been reported by Gold (1969) in workers contacting tetrachloroethylene.

Other cases of chemical burns resulting from tetrachloroethylene have been reported by Weiss (1969) and Morgan (1969). Rowe et al. (1963) have reported skin irritation with exposure in rabbits.

Therapeutic Uses

Extensive oral exposure to tetrachloroethylene is not new. Hookworm treatment with oral tetrachloroethylene was popular in the 1920's and 1930's in India and the Pacific Islands. Kendrick (1929) treated 1,500 prisoners in the Madras jails and reported one severe case of toxicity, after a three milliliter oral dose, where the patient became unconscious for 3 hours but recovered. An average "worming dose" to the human prisoners of 0.15 ml/kg was reported.

Lambert (1933) gave 46,000 hookworm treatments in the South Pacific Islands with no deaths from oral tetrachloroethylene and reported fewer toxic symptoms that from other anthelmintics. A review in the late 1930's stated that 100,000 treatments for hookworms had been given without a death.

In India, Fernando et al. (1939) gave tetrachloroethylene to a large group with confounding pathologies and who ranged from one year of age to 70. Tests were run that would identify severe liver damage, hemolysis or renal pathology as a result of the tetrachloroethylene dosage. Six milliliters to adults frequently produced giddiness. Elevated bile pigments were seen in the urine of some patients, particularly those with malaria and anemia. Children tolerated doses of "four to five times their age in minims" which is about five drops of tetrachloroethylene orally for every year of age. The Fernando paper reported effects in 11 subjects who were given 6.0 to 8.0 ml orally:

1 of 11 had a drop in blood pressure from 135/80 to 112/70

1/11 was semiconscious for 4.5 hours

4/11 had considerable depressant effects: sleepiness, faintness, drowsiness

11/11 were giddy; and

0/11 had "appreciable" liver or kidney toxicity

The only serious narcotic effect, noted above, occurred in a man whose weight was so low that the oral dose was "0.21 ml/kg body weight." Four milliliters of tetrachloroethylene was reported to cause no "untoward effect" in any subjects, and that was the usual dose.

It is noted, however, that although the doses were high and the number of humans exposed was large, the use of tetrachloroethylene in worm medication was usually a single, acute exposure.

Table VI-2 summarizes effects of acute or subchronic exposure in humans to PCE (U.S. EPA, 1979).

Short-term/subchronic

Experimental studies

Stewart, et al. (1977) examined a group of 12 volunteers exposed to 168 and 670 mg PCE/m^3 (25 and 100 ppm) for 5-1/2 hours a day repeated up to 55 training and exposure days over 11 weeks. In this study, they were unable to document any consistent neurologial changes due to PCE exposure, although they did observe a statistically significant decrement in the performance of a Flanagan coordination test (which the authors stated as being non-consistent).

Accidental exposure

Lob (1957) briefly described what he considered to be benign cases of exposure occurring in workers involved in the cleaning of metal parts. The individuals were exposed for a period of three weeks to five months. In each case, the symptoms were similar: fatigue, feelings of inebriation, dizziness, headache, nausea, vomiting, lack of appetite, sleeplessness, irritability and occasionally coughing or irritation of the eyes. All of the symptoms disappeared quickly when the worker left the work site.

Table VI-2

EFFECTS OF ACUTE OR SUBCHRONIC EXPOSURES TO TETRACHLOROETHYLENE IN HUMANS

Concentration (ppm)	Exposure time	Reported effects					Urinary metabolites
		Eyes	CNS	Resp.	Liver	Heart	
20-70	Occasionally daily						D
75-80	1-4 min						
106	4 hr						
100	7-1/2 hr/day		D[1]				
100-120	4-6 min			S-M			
150	7-1/2 hr/day		S-M[2]				
10-400	8 hr/day, 5 days/week						S-M
216	2 hr	D	S-M	D			
50-250	Occasionally daily		M-S[3]				
50-250	Daily, 4 month		D				
50-250	Daily, 5 months		D	S-M	S-L[4]	S-L	
210-244	30 min		S-M				
280	2 hr	S-M	M-S				
232-385	8 hr, 2 times/week				S-L		
200-400	Occasionally daily						M-S
25-1,470	3-1/2 hr	M-S	M-S		M-S		
475-680	30 min	D	M-S	D			
513-690	10 min	S-M	M-S	S-M			
934-1,140	95 min	M-S	S-L	S-M			
930-1,185	1-2 min	S-L	S-L	S-M			
2,000	7-1/2 min		S-L				

[1] Detectable
[2] Slight--->moderate
[3] Moderate--->serious
[4] Serious--->lethal

Hughes (1954) reported a single case of liver toxicity with nausea, jaundice and grossly abnormal liver function tests (undescribed) in a young man exposed for approximately 3 months to high levels of tetrachloroethylene. Examination four weeks after hospitalization revealed continued impaired liver function. Ten months after the illness, the man experienced nausea after brief tetrachloroethylene exposure.

Another case of industrial exposure was described by Eberhardt and Freundt (1966). Two months' exposure while cleaning metal parts with tetrachloroethylene produced symptoms of numbness, dizziness and anorexia in a 65 year-old female. The concentration inhaled and extent of skin contact were undisclosed in the report. Recovery occurred following 8 days' absence from exposure.

A woman working with tetrachloroethylene in a dry-cleaning plant as long as 10 hr/day for 2.5 months (no measure of workplace air concentration) was reported to have liver toxicity by Meckler and Phelps (1966). Diagnosis was made by increased alkaline phosphatase, SGOT, bilirubin and cephalin flocculation measurements which were all consistent with liver disease. Liver biopsy two weeks afer exposure showed showed degeneration of parenchymal cells, focal collections of mononuclear cells and exaggeration of liver sinusoids. The liver was still enlarged six months later.

The death by cardiac or toxic pulmonary edema of a 23-year old man reported by Trense and Zimmerman (1969) followed four months of working with high levels of tetrachloroethylene (about 250 ppm). At autopsy, an enlarged liver with hepatic cell necrosis and fatty degeneration of the myocardium were found. Chlorinated hydrocarbons were not found in the liver.

Medical World News contained a report of a six-week-old baby with jaundice and an enlarged liver; the baby was breast-fed by a mother who frequently inhaled tetrachloroethylene in a Canadian dry cleaning establishment (Anonymous, 1978). The mother's milk contained tetrachloroethylene levels up to 10 mg/l. The child's symptoms vanished when breast feeding was discontinued. It was noted that while adults metabolize and excrete these chlorinated solvents readily at low levels, the enzyme systems in a six-week-old child may not be adequate for detoxification.

Longer-term Exposure

As suggested by Stewart, et al. (1970), the threshold limit value of 100 ppm for PCE (ACGIH, 1977) has a negligible factor of safety even for short-term exposures. In 1981, the change to 50 ppm was proposed (ACGIH, 1981). That more serious central nervous system problems may be associated with chronic PCE exposure is suggested by a few sporadic case reports (Gold, 1969) and small scale epidemiological and clinical studies (Coler and Rossmiller, 1953). However, the latter studies have often been complicated by exposures to other solvents (Tuttle, et al., 1977).

Coler and Rossmiller (1953) described longer-term exposures experienced by seven men who worked in degreasing operations with tetrachloroethylene at 230 to 385 ppm (1900-2600 mg/m^3) two days a week for two to six years. All seven exhibited memory impairment, staggered gait and a drunken-like state. They complained of lightheadedness, dizziness, tiredness and a feeling of intoxication with the accompanying hangover. Their symptoms were aggravated by high humidity. Medical histories taken in the presence of the plant manager revealed no extensive alcohol consumption by any worker, but one of the seven had a gastric hemorrhage and cirrhosis of the liver. Three of the seven were found to have impaired liver function as diagnosed by sulfobromophthalein sodium dye retention; four of the seven had positive urobilinogen.

Two case reports were described by Lob (1957) in which long-term exposure to tetrachloroethylene resulted in irreversible neurological effects. In the first case, a middle-aged male experienced nearly continuous exposure in the workplace followed by intermittent exposures for two more years in a metal cleaning operation. Symptoms began to appear at the end of the fourth year, characterized by gastrointestinal disturbances, abdominal pain and severe frontal headaches. Two years after cessation of exposure, upon hospitalization, the individual exhibited continued gastrointestinal troubles, neuroautonomic dystonia, virile climacterium and mental depression. Soon thereafter, labyrinthine disorders were noted, followed by memory loss, somnolence and insomnia, yawning attacks, slight motor incoordination and abnormal reflexes.

In the second case described by Lob (1957), an individual in his late 30's was exposed to trichloroethylene for six months, then to tetrachloroethylene for a year in a metal cleaning operation. Measurement of tetrachloroethylene vapor concentrations around the open tub were about 75 ppm; this determination, however, was done after improved ventilation measures were instituted. The man complained of headaches and dizziness which would disappear overnight. Over the next year, his symptoms persisted and became aggravated. Other symptoms became evident, including fatigue, anorexia, nausea, loss of libido and intolerance to alcohol. Employment ended at this point, but within three months, he experienced gait problems and numbness, sweating and alternating blanching and flushing of the fingertips (intermittent claudication indicative of Reynaud's phenomenon). His neurological disturbances progressed to trembling and weakness of the extremities with hyperreflexia, increased muscle tone of the legs, equilibrium and gait disturbances. Some liver effects were seen as positive reactions and were noted for urobilin, urobilinogen and bilirubin in the urine. A year later, his status remained essentially the same, with continued neurological symptoms.

A case report by Gold (1969) suggests serious nervous system effects in one exposed subject. A 47 year-old male, who owned a dry cleaning establishment, worked daily for three years around the fumes. On Sunday he would clean the tanks, apparently being subjected to high exposure levels, after which he would literally stagger home and sleep or pass out for a couple of hours, during which time he could not be roused. His acute symptoms included nausea, vomiting, dizziness, staggered gait and disorientation. Chronically, he exhibited difficulty remembering recent events, mild disorientation, mood lability and fatigue, with symptoms persisting at least one year after exposure ceased. The clinical picture suggested both basal ganglia involvement and cerebral cortical damage.

Palecek (1970) reported asthma induced by exposure to tetrachloroethylene in a 55 year-old woman who had owned a dry cleaning establishment for more than two years. Two massive exposures, occurring a year apart, induced an acute reaction each time. Both exposures were accompanied by asthmatic coughing attacks. During the second incident, she became unconscious. After these two incidents, she developed asthmatic attacks whenever she was in the shop. The diagnosis of asthma was made when: (a) the rate of exhaled air decreased from 4.6 to 2.8 liters/sec, and (b) a positive reaction occurred in an acetylcholine test.

Occasional reports have associated PCE with the symptomatology of more serious chronic diseases such as Raynaud's disease (Lob, 1957; Sparrow, 1977). Sparrow (1977) has reported a case which involved depressed immune function, mildly depressed liver function, polymyopathy and severe acrocyanosis. Such isolated reports are difficult to evaluate, but deserve mention here because of a similar disease which has been observed in vinyl chloride workers. Vinyl chloride, or monochloroethylene, is closely related to PCE. The case reported by Sparrow had no known exposure to vinyl chloride.

Lassota (1975) has suggested that a dependency for tetrachloroethylene may develop when the solvent is misused as a drug (e.g., to "get high"). He reported on a patient who had sniffed the chemical two to three times per week, as much as a 200 ml bottle each time over a six-month period. Prior to sniffing tetrachloroethylene, he had sniffed trichloroethylene occasionally over a period of one and one half years. The patient reported that his desire for the chemical increased after alcohol consumption. After an extended period of use, he reported blood in the mouth, trouble in concentrating, trembling hands, sensory disturbances (sight, hearing, smell and touch), talking to himself in a critical manner, and an increased desire for the chemical. In the hospital, he was trembling and showed antisocial behavior. He had a bottle of tetrachloroethylene hidden in his room. During his chemical intoxication, he hallucinated and exhibited equilibrium disturbances. A second patient with a history of multiple drug abuse reported in Lassota's study also was using tetrachloroethylene. While intoxicated with the chemical, he hallucinated but did not exhibit any equilibrium disturbances. In the hospital, he had dilated pupils, a decrease in muscular tension, quick reactions and a sense of terror.

Table VI-3 summarizes the literature reporting the effects of tetrachloroethylene in humans.

Epidemiologic studies

Because tetrachlorethylene is used as a dry cleaning solvent, a commercial solvent and a degreasing solvent, exposure of workers to low level concentrations frequently occurs. It has been suggested that the hazard of tetrachloroethylene exposure has gone unrecognized in the industrial setting and that work practices for safety have been largely unimplemented. While few epidemiologic studies have been done to date to determine the potential for hazard to health from exposure to low levels of the substance in the industrial setting, the need for doing so has finally been recognized and efforts are being made to evaluate more fully the health effects that might be expected to arise from exposure in the workplace.

Franke and Eggeling (1969) conducted an occupational health study of 113 workers from 46 chemical cleaning plants. Three hundred forty-two (342) measurements of air concentrations of PCE were made in these plants, including measurements at 15 minute-intervals in two of the shops.

TABLE VI-3

SUMMARY OF EFFECTS OF TETRACHLOROETHYLENE IN HUMANS

	Route	Dose	Length of exposure;effects	Reference
Human	Oral	3 ml	Mild transient gastrointestinal reactions	Mutalik and Gulati (1972)
Human	Inhalation	75-80 ppm	1-4 min: slight transient eye irritation	Stewart et al. (1961b); Carpenter (1937); Rowe et al. (1952)
Human	Inhalation	100-120 ppm	1 hr: soft palate irritation accompanied by dryness; mild eye irritation	Stewart et al. (1961b); Carpenter (1937); Rowe et al. (1952)
Human	Inhalation	230-385 ppm	2 days/week, 2 1/2 to 6 years: severe gastric hemorrhage and cirrhosis of the liver; signs of liver dysfunction	Stewart et al. (1961b); Carpenter (1937); Rowe et al. (1952)
Human	Inhalation	475-600 ppm	2 hr: increased salivation, increased perspiration of hands, increased secretion of mucous from the nasal passages, numbness about mouth, mental effort needed for good motor coordination	Coler and Rossmiller (1953)
Human	Inhalation	1,000 ppm	1 hr, 35 min: marked irritation to eyes and upper respiratory tract; lassitude, mental fogginess, anesthetization of lips and tip of nose, exhilaration, congestion of the eustachian tubes	Stewart et al. (1961b); Carpenter (1937); Rowe et al. (1952)

TABLE VI-3 (Continued)

Route		Dose	Length of exposure:effects	Reference
Human	Inhalation	1,500 ppm	Immediate:faintness, aching facial muscles; dyspnea upon exertion, mental sluggishness, slight inebriation and slight effect upon physical balance noted after exposure	Stewart et al. (1961b); Carpenter (1937); Rowe et al. (1952)
Human	Inhalation	High	Acute: pulmonary edema	Lob (1957); Patel et al.(1973)
Human	Inhalation	High	Acute: transient liver damage	Stewart et al. (1961b); Stewart (1969); Saland (1967)
Human	Inhalation	High	Unconsciousness; death	Stewart et al. (1961); Lob (1957); Ling and Lindsay (1971); Morgan (1969); Stewart (1969); Saland (1967); Braddock (1965); Patel et al.(1973)
Human	Inhalation	High (250 ppm)	4 months: hemoptysis, coughing, sweating attacks, jaundice, oliguria, hematemesis, cardiovascular failure and death	Trense and Zimmerman (1969)
Human	Skin contact	Liquid	30 min: burns, erythema, blistering	Ling and Lindsay (1971); Morgan (1969)

Source: U.S. EPA (1979)

The exposed workers included 55 males and 58 females. Forty-three (43) control workers were fire department personnel at a rubber plant or patients under supervision for dust control.

The concentration of PCE in the air reached a maximum of 400 ppm (2700 mg/m^3) with 75% of the 326 random samples measuring 100 ppm or less (680 mg/m^3).

Physical examinations including liver function tests and analyses of trichloroacetic acid in the urine were conducted, and a list of complaints was obtained. Significant differences were found between exposed and unexposed individuals in thymol turbidity and bilirubin determinations, changes attributed to exposure to the tetrachloroethylene. The duration of exposure and maximum PCE concentration did not appear to be related to the laboratory findings. The authors concluded that PCE exerts a toxic effect on the liver. They found that exposure to PCE was associated with complaints similar to those described by Grandjean (1959). These included: headaches, dizziness, fatigue, psychological irritation, insomnia and occasional numbness of the extremities. Forty-five out of the 113 workers showed evidence of autonomic lability such as hyperhydrosis, dermographism, reflex problems or tremor. Apparently, the control group was not examined to determine the presence of these symptoms.

Medek and Kovarik (1973) examined 77 workers from several industries. The tetrachloroethylene-exposed group consisted of 35 females and 5 males. Of these, 14 were chemical clothes cleaning employes and 26 were employed in metal degreasing operations. Their ages ranged from 21 to 68 years. Twenty-six of the 40 had been exposed for three years; the longest exposure was of a female exposed for 15 years. The unexposed control group was made up of 37 glass cutters, similar in sex and age to the exposed workers.

Tetrachloroethylene levels in most of the workshops were determined to be approximately 400 mg/m^3 (59 ppm), with one measured excursion up to 913 mg/m^3 (135 ppm). Seventy-three percent of the 40 workers exposed to the vapor complained of headaches, fatigue, sleepiness, dizziness and feelings of drunkenness. Urinary metabolites were found to be trichloroacetic acid (mean = 16.3 mg/l; maximum= 41 mg/l) and trichloroethanol (mean = 40 mg/l; maximum = 116 mg/l). Forty-five percent of the exposed workers had objective neurological symptoms (trembling of the eyelids and fingers and a positive Chvostek sign). Neither period of exposure nor age had an effect upon the occurrence of symptoms. Of the control group, 14, or 38 percent, had neurological symptoms. The two groups were not significantly different in terms of these symptoms. The subjective complaints of the exposed group were similar to those reported by other investigators.

The effects of tetrachloroethylene on the behavior and neurological status of 27 volunteers from five laundry and dry cleaning plants were measured (Tuttle, et al., 1977).

Eighteen workers were exposed daily to 18 ppm (122 mg/m^3), calculated as an eight-hour time-weighted average (TWA) over five days of testing. Nine male members of this group had a mean exposure of 32 ppm (217 mg/m^3). The exposure for the men was higher than for the females because five of them were dry cleaning machine operators. The control group was made up of nine female laundry workers in one of the plants who were assumed to be unexposed to tetrachloroethylene. However, one of the nine had previously been exposed to PCE for one year.

Among those in the exposed group, four men had previously been exposed to petroleum products for an average of 16 years; one woman had been exposed to petroleum solvent for 21 years, one man to carbon tetrachloride for five years, and one man to carbon disulfide for ten years previously. The nine exposed males had a mean exposure duration of 9.8 years; the nine exposed females averaged 6.7 years of exposure.

Before testing, a medical history questionnaire and medical exam were completed. The medical exam included a neurological exam, electromyography (EMG)/nerve conduction exam, blood sugar and hematocrit to determine a Total Neurological Score. The behavioral test battery was administered and breath samples were taken at the beginning and end of each day; breath samples also were taken at two hour intervals, and air samples four times a day at each work station.

Eight tests were administered as part of an experimental test battery:

1. Feeling tone checklist
2. Wechsler digit span
3. Wechsler digit symbol
4. Neisser letter search
5. Critical flicker fusion
6. Santa Ana dexterity test
7. Choice reaction time
8. Simple reaction time

The reaction time tests were added since some neurotoxins slow nerve conduction velocity and movement time, and these test should quantitate such effects.

A difference was noted ($p < 0.10$) between neurological ratings for the tetrachloroethylene-exposed workers versus controls. Statistical analysis, however, showed these test results correlated better with earlier exposure to a Stoddard solvent rather than to the current tetrachloroethylene exposure.

In one of the behavioral tests, a post-shift decrement was noted; this test was said to be correlated with a measure of fatigue and not PCE exposure. On the whole, the authors' results showed little evidence of post-shift performance decrement of fatigue effects.

This study was an good pilot study, examining the use of several behavioral tests to evaluate nervous system effects. The authors found that PCE did not adversely affect the workers' neurological health or performance. The design of their exposure ascertainment was excellent and effects ascertainment was good, but the criteria for inclusion in the study were poor (i.e., previous exposure to other substances) and the sample examined too small and diverse that no conclusion can be drawn concerning the effects of extended exposure to PCE alone.

In a preliminary report, Blair, et al. (1979) compared the relative frequency of specific causes of death in a group of former laundry and dry cleaning workers with the experience of the general population. As a part of a larger cohort mortality study, mortality records for the period 1957 to 1977 were obtained from two laundry and dry cleaning union locals. Three hundred thirty (330) decedents were identified from death benefits lists, reports of relatives and friends and obituary listings. These sources were not assumed to represent a complete listing of death among individuals belonging to those locals. Union records indicated that 279 of the individuals had worked exclusively at dry cleaning shops while they had been union members. Death certificates were obtained for these. Sex, race, age at death and underlying and contributing causes of death were abstracted from each certificate.

The increased proportion of cancer deaths found resulted from an excess of lung and cervical cancer and slight excesses of leukemia and liver cancer. The authors stated that the small number of deaths examined, the possible biases in the set of decedents obtained and the limitations of the proportionate mortality ratio method permitted only cautious interpretation of the study results.

The low wage scale for the laundry and dry cleaning workers may mean that other well-known epidemiologic factors are producing the excess in cancer in this group when it is compared, not to identical controls, but to the population of the United States as a whole. Additional caution is necessary in interpreting the data and ascribing any effects to tetrachloroethylene. It was noted that, in the 10,000-cohort study, there was no distinction between those shops using tetrachloroethylene and those using carbon tetrachloride, trichloroethylene or other petroleum solvents. Although multiple chemical exposures may have occurred, tetrachloroethylene has been the most frequently used solvent for 20 to 25 years and is used by approximately 75 percent of the present plants according to the study.

Ludwig (1979) described an industry-wide study being conducted by the National Institute for Occupational Safety and Health (NIOSH) to assess the health effects of occupational exposures to tetrachloroethylene. Industrial hygiene surveys were conducted at 45 retail dry cleaning facilities in five states to document exposure levels for use with the mortality study. The cohort consists of 1,600 individuals selected from union records and exposed to PCE for at least one year beginning prior to 1960. The initial status of each person in the cohort will be determined and the observed deaths will be compared with those expected based upon a standard race, sex and age specific population. Individuals with previous occupational exposure to carbon tetrachloride or trichloroethylene in the dry cleaning industry, based upon union records, have been excluded from the cohort to eliminate possible confounding factors.

A study by Kaplan (1980) on dry cleaners exposed to perchloroethylene has become available. No conclusions can be drawn from the study because of a number of deficiencies in it. Therefore, extensive discussion of the study is not included in the body of this document.

Summary

As with experimental animals, the most characteristic response in humans to an acute exposure to tetrachloroethylene is depression of the central nervous system. While anesthetic concentrations can be reached in air, few deaths could be documented as having been due to tetrachloroethylene exposure. All narcotic symptoms appear to be reversible. Transient liver and kidney dysfunction has been noted in some cases.

Reported short-term/subchronic exposures usually consist of repeated exposures over several months which result in periods of apparent CNS depression, usually without narcosis. Symptoms often manifested are inebriation, dizziness, fatigue, anorexia and insomia. The effects reverse within minutes to hours after the exposed individual is removed from contact with the substance. With somewhat higher levels of exposure, hepatic toxicity can be expected. Liver changes may take several months to revert to normal.

Upon chronic exposure, the possibility of chronic nervous system damage increases. Although not well-documented to date, indications are that permanent neuropathies may result from long-term exposure to tetrachloroethylene. Hepatic damage can be persistent. Some question has arisen as to the capability of tetrachloroethylene to induce diseases such as Raynaud's phenomenon or the complex of symptoms observed in workers exposed to vinyl chloride. Occasional idiosyncratic responses such as pulmonary edema, asthma, hypersensitivity or dependency have been reported.

Few good epidemiologic studies are available from which definitive conclusions concerning the long-term effects of tetrachloroethylene can be made. Some studies are complicated by the fact that the individuals under study have been exposed to other structurally-similar solvents, either previously or coincidentally. The preliminary report on the mortality profile of dry cleaning workers suggests that there may be an excess of certain kinds of cancers in the exposed population. However, greater consideration of confounding factors must be given before a true association can be established between the increase in occurrence of cancer and exposure to tetrachloroethylene.

The odor threshold in air for tetrachloroethylene is 50 ppm for previously-unexposed individuals. With increasing exposure, both in terms of duration of a single exposure and numbers of repeated exposures, the threshold for detection rises.

The only experience we have with tetrachloroethylene exposure by the oral route is in its use an an anthelminthic. The few reported studies of wide-scale use for the treatment of hookworm and other gastrointestinal infestations suggest that the substance is relatively innocous by the oral route. However, it is not possible to derive a human no-effect level for acute oral exposure from these old clinical reports.

A well-controlled study of the effects observed over a range of acutely-applied vapor concentrations of tetrachloroethylene was that of Rowe, et al. (1952) in which the investigators exposed volunteers to increasing concentrations from 100 to 1200 ppm. Subjective and objective responses were noted. Slight discomfort was noted at the lowest dose in one out of six individuals. Doubling the concentration resulted in sinus congestion in all subjects. Tripling the concentration was discomfiting to all, each of whom suffered CNS depressant effects of lightheadedness, inebriation, etc. Stewart and his coworkers have suggested that behavioral changes may take place at concentrations equivalent to the now-former TLV of 100 ppm. Reevaluation of this standard by the ACGIH resulted in a proposed change to 50 ppm (ACGIH, 1981).

VII. Mutagenicity/Carcinogenicity

Mutagenicity

Only one laboratory has published positive results in assays measuring the mutagenic potential of tetrachloroethylene, although a number of studies have reported negative results. There is also one unpublished report showing positive results with the stabilized compound (Margard, 1978).

Cerna and Kypenova (1977; abstract only) reported elevated mutagenic activity in a *Salmonella* strain (TA 100) sensitive to both base substitution and frameshift mutation. Dose dependence was observed with concentrations of 0.01, 0.1 and 1.0 mg/l. In host-mediated assays employing TA 1950, TA 1951, and TA 1952, the number of revertants increased significantly at dose levels equal to or half of the LD_{50} (strain of mouse not cited). Cytogenetic analysis of mouse bone marrow was performed 6, 24 or 48 hours after the last of a single or multiple application of PCE (one application per day for five days). No significant increases in chromosomal aberrations were noted at a dose equal to half of the LD_{50} (again, the strain was not cited). It also is impossible to determine if the PCE used was pure or stabilized. The positive responses may be due to an added stabilizer.

Henschler (1977a,b) and co-workers (Bonse, et al., 1975; Greim, et al., 1975; Bonse and Henschler, 1976; Henschler and Bonse, 1977) have postulated that the reactivity of the metabolically-formed epoxide intermediates determine the potential for mutagenicity and carcinogenicity of the chlorinated ethylenes. According to this hypothesis, those substances with unsymmetrically substituted chlorine atoms (such as vinyl chloride or 1,1-dichloroethylene) form more reactive intermediates and thus are potentially mutagenic or carcinogenic. Those substances, such as tetrachloroethylene or 1,2-dichloroethylene are balanced and thus would not be expected to be mutagenic or carcinogenic.

Support for this hypothesis is gained from the demonstration of an increased rate of spontaneous mutation in _E_. _Coli_ K_{12} in the presence of liver microsomes when treated with chloroethylene (vinyl chloride), 1,1-dichloroethylene and trichloroethylene and an absence of an increased rate of mutation with the symmetrically substituted 1,2-dichloroethylenes and tetrachloroethylene (Greim, et al., 1975; Henschler and Bonse, 1977).

Two _in vitro_ test systems were used in the mutagenicity tests on tetrachloroethylene (and other solvents) by Greim et al. (1977). Both microsome-activated and unactivated TA 1538 and _E_. _coli_ K_{12} were used for measuring frequency of reversion. Peripheral human lymphocytes (microsome activated) were used as target cells for evaluation of chromosomal aberrations. Tetrachloroethylene was not activated to a mutagenic form in these tests.

Bartsch, et al. (1979) tested tetrachloroethylene, along with several other similar compounds, using the plate incorporation assay as modified for gaseous or volatile chemicals. PCE caused no concentration and/or microsome dependent increase in the number of mutant colonies in S. typhimurium TA 100 with concentrations up to 4 x 10^{-4}M in the presence of a liver S-9 fraction from phenobarbital-treated mice, with or without the cofactors, G6-P dehydrogenase and $NADP^{++}$. Concentrations above 5 x 10 $^{-4}$M were toxic to the organisms. PCE was the only substance among those tested that was not mutagenic, but for which positive carcinogenicity data in animals or man are available. Vinyl acetate was not mutagenic, and does not produce tumors in rats (Maltoni and Lefemine, 1975). On the other hand, vinyl chloride was shown to be mutagenic as well as capable of inducing tumors in rodent and human liver (IARC, 1979). Trichloroethylene induces hepatocellular carcinomas. 1,4-Dichlorobutene-2 and epichlorhydrin induce local sarcomas in mice (IARC, 1977). Each of these substances was mutagenic in the present study.

Rampy et al. (1978) reported on the cytogenetic analysis in bone marrow smears from male rats exposed to 0, 300 or 600 ppm tetrachloroethylene 6 hours a day, 5 days a week for 12 months. Three rats from each exposure level were sacrificed and the bone marrow cells were examined for chromosome or chromatid aberrations on the day exposure was terminated. No cytogenetic effects were detected in the male rats. Low numbers of available marrow cells made interpretations impossible in the female rats.

Ikeda, et al. (1980) examined lymphocytes from 10 factory workers who had been exposed to tetrachloroethylene for 3 months to 18 years. These cells were observed for possible chromosome aberrations, increased rate of sister chromatid exchange and modified cell cycle kinetics. Workroom air levels of tetrachloroethylene ranged from 30-220 ppm (geometric mean=92ppm) for 6 exposed workers in the degreasing facilities (Group 1). The 5 males in this group had work histories of exposure of 10-18 years. The lone female in this group had been exposed for 2 years. Group 2 consisted of 2 males and 2 females in a support department with lower exposures (10-40 ppm, with rare peaks up to 80 ppm) and shorter work histories (3 months-3 years). A control group of 6 males and 5 females was studied concurrently.

Urinalyses for total trichloro compounds were 50.7 mg/l (range=41.1-62.2 mg/l) in Group 1 and 19.0 mg/l (range=14.8-24.4 mg/l) in Group 2. None was detected in the urines of the control group.

The findings of the exposed workers of either group did not differ significantly from those of the controls with respect to the frequencies of chromosome or chromatid aberrations (numerical or structural) and sister chromatid exchanges. Cell cycle kinetic parameters (the proportion of M_2 + M_3 metaphases and mitotic index) were also essentially the same for all three groups. The aberrations observed were primarily gaps and/or breaks of chromosome and chromatids; more severe abnormalities were not observed. Possible differences in susceptibility to mitomycin C (10^{-8} M) were tested. There was no elevated frequency of aberrations (numerical or structural) after mitomycin-C treatment of lymphocytes from the exposed workers. The controls did show a significant increase (P 0.025). The SCE increases, after mitomycin C treatment, were essentially uniform across all groups. Treatment did not induce significant changes in proportions of $M_2 + M_3$ metaphases or mitotic index.

A study by Callen, et al. (1980) evaluated the mutagenic potential of tetrachloroethylene stabilized with 0.01% thymol on cultures of Saccharomyces cerevisiae D7. A marginal increase in the frequency of gene conversions, mitotic recombinations and reversions was produced by a one-hour treatment at 4.9 mM. A greater increase in gene conversion and mitotic recombination was observed at 6.6 mM. However, since no concurrent thymol control was run in this experiment, one cannot state with certainty that the tetrachloroethylene was responsible for the observed changes.

A summary of the results of testing PCE in short-term assay systems can be found in Table VII-1.

TABLE ~~III~~ VII -1

RESULTS OF TESTING TETRACHLOROETHYLENE IN SHORT-TERM ASSAY SYSTEMS

Assay System	Effect Measured*	Results†	Reference
A. Prokaryotic Mutagenesis	G		
Salmonella		+ in TA 100	Cerna and Kypenova (1977) (abstract only)
		- in TA 1538 (with (and without S-9)	Greim, et al., 1977
		+ (with stabilizer) - (without stabilizer) (TA 98, TA 100, TA 1535, TA 1537, TA 1538)	Margard, 1978
		- in TA 100 (with S-9, (with and without G6PD and NADP)	Bartsch, et al., 1979
E. coli K_{12}	G	- (with S-9)	Greim, et al., 1975, 1977 Henschler and Bonse, 1977
B. Host-mediated Assay (TA 1950, TA 1951, TA 1952 in mouse)	G	+ (# of revertants measured)	Cerna and Kypenova, 1977 (Abstract only)

* G = Genotoxic; NG = Non-genotoxic

† + = positive; - = negative

VII-2
TABLE ~~III~~ (cont'd)

Assay System	Effect Measured*	Results†	Reference
C. Saccharomyces cerevisiae			
	G	+ (gene conversion, reversions)	Callan,et al., 1980
	NG?	+ (mitotic recombination) [Results uncertain because substance stabilized with thymol; no thymol control]	
D. Cell transformation			
Fischer rat embryo (F1706)	NG?	+	Price, et al.,1978
E. Pulmonary tumor induction in Strain A mouse	G	-	Theiss, et al., 1977
F. Cytogenetics	NG?		
Human lymphocytes		-	Greim, et al., 1977
Human lymphocytes: 10 occupationally-exposed workers		-	Ikeda, et al., 1980
Mouse bone marrow smears		-	Cerna and Kypenova, 1977. (Abstract only)
Rat bone marrow smears		-	Rampy, et al., 1978

TABLE ~~III~~ VII - 9 (cont'd)

Assay System	Effect Measured*	Results†	Reference
G. DNA synthesis (Uptake of [^{3}H]-thymidine)	NG?		
Mouse liver		+ (2 fold increase)	Schumann, et al., 1980
Rat liver		-	Schumann, et al., 1980
H. DNA binding	G		
Mouse liver		-	Schumann, et al., 1980
Rat liver		-	Schumann, et al., 1980

Carcinogenicity

The National Cancer Institute Carcinogenesis Bioassay report for tetrachloroethylene was released in October 1977 (NCI, 1977). This report presented results of a 2-year bioassay for possible carcinogenicity of tetrachloroethylene using Osborne-Mendel rats and B6C3F1 mice. USP-grade tetrachloroethylene in corn oil was administered by gavage to groups of 50 male and 50 female animals at either of two time-weighted average dose levels: male rats, 471 and 941 mg/kg, female rats, 474 and 949 mg/kg, male mice, 536 and 1,072 mg/kg and female mice, 386 and 772 mg/kg. These doses were administered 5 days/week for 78 weeks. Untreated controls and vehicle control groups consisted of 20 animals of each species and sex; the vehicle control animals were dosed with the corn oil only in the amounts given the high dose animals. After the 78-week period, rats were observed for 32 additional weeks (a total of 110 weeks) and mice were observed for 12 additional weeks (a total of 90 weeks). About 30 tissues from almost all of the animals were prepared for microscopic evaluation.

Under these conditions, NCI determined that tetrachloroethylene was a liver carcinogen in B6C3F1 mice. The data do not indicate that tetrachloroethylene causes cancer in Osborne-Mendel rats. Definitive results were impossible to evaluate because of high mortality during the study. A significant increase in hepatocellular carcinoma was seen in both sexes of treated mice when compared to control animals. Hepatocellular carcinomas were observed in 32/49 (65%) of the low dose males, 27/48 (56%) of the high dose males and 19/48 (40%) of both low and high dose females. These tumors were seen in 2/17 (12%) of the untreated or 2/20 (10%) of the vehicle-dosed control male mice. Two of 20 (10%) untreated control females and no vehicle control female developed hepatocellular carcinomas.

The tetrachloroethylene doses used were toxic to the kidneys of the Osborne-Mendel rats in this study. The final report (NCI, 1977) noted toxic nephropathy and death as early as week 20 of the study. This toxic effect was dose-related; half the high dose male rats were dead by week 44 and half of the females by week 66.

It was concluded by the NCI review committee that these results produced no evidence for tetrachloroethylene carcinogenicity in the rats that survived the doses. Because of the difference in death rates in the control and experimental groups, there does exist a statistical possibility that the results would have been different had survival been equal in the groups. Partly because of this possibility, the bioassays are being repeated. On the other hand, there was early death in the mice on bioassay, and survivors of both sexes showed statistically significant tumor incidences. Analysis of the mouse data gives the early mortality shown below in Table VIII-2 which suggests that the optimum dose was exceeded. Nevertheless, specific liver tumors were found in a substantial number of the mice that died early in the experiment.

TABLE VII-2

MEAN SURVIVAL TIME: B6C3F1 MICE

	High Dose	Low Dose	Controls
Male	42 weeks	78 weeks	Over 90 weeks
Female	50 weeks	61 weeks	Over 90 weeks (the termination of the experiment)

(NCI, 1977)

A review of the NCI data indicates that the response of male mice appeared to be greater than that of female mice not only in total incidence but in shorter latency (see Table VII-3)

TABLE VII-3

TIME-TO-TUMOR (B6C3F1 MICE) (in weeks)

	High Dose	Low Dose	Controls
Male	40	27	90 and 91
Female	50	41	91

This sex difference in toxicity may not be a real one; control males also had a higher tumor incidence and shorter latency.

There were several design features that furnish potential weaknesses in these bioassay results. Several of these potentially modifying or contributing features are acknowledged in the NCI report, such as:

1. Ninety-three percent of the mice exhibited clinically evident toxic nephropathy during most of the study.
2. Clinical signs of toxicity were seen in all dosed rats. Seventy-nine percent of the dosed rats showed toxic nephropathy.
3. Very high death rates occurred among the treated rats. Half of the high dose male rats died by Week 44; half of the high dose females died by Week 66.
4. Rats had chronic respiratory disease.
5. Groups of animals which had received other volatile chemicals were housed in the same room, presenting the possible chance of animal exposure to very low levels of other compounds.
6. Unique species differences in susceptibility to toxicity were seen, with high sensitivity of the B6C3F1 mouse and low sensitivity of the NCI Osborne-Mendel to tetrachloroethylene (and most chlorinated aliphatic compounds). A strongly-evident species difference in metabolism may indicate aberrancies in the toxification or detoxification processes. Species differences in tissue binding, inactivation,

clearance, or epoxide-forming enzyme levels could all influence the experimental data relevance.

7. Dose levels, the maximum tolerated doses, (MTD) have been further clarified since the protocol was established. The very high levels (the highest consistent with long-term survival) have been critized as possibly producing unique metabolites in animals through metabolic paths that are not normally functional. Further, the toxic effects of such high doses could either enhance or inhibit carcinogenesis by several potential means.

Two more 2-year carcinogenesis bioassays of tetrachloroethylene, sponsored by NTP, are nearly complete. The chronic gavage study is being run on four rat strains and one mouse strain. The second study is an inhalation study in one rat strain and one mouse strain. In these studies, the test compound contained no stabilizers.

Some other work has been done on the carcinogenicity of tetrachloroethylene. Theiss et al. (1977) dosed male strain A mice intraperitoneally with tetrachloroethylene at total doses of 80, 200 or 400 mg/kg administered three times weekly for 5 or 8 weeks. The survivors, sacrificed 24 weeks after the last dose, did not show an increased incidence of lung tumors over controls.

An unpublished chronic inhalation study by Dow Chemical Company (Rampy et al. 1978) also has examined the carcinogenicity of tetrachloroethylene. This study found that neither 300 nor 600 ppm tetrachloroethylene (as a commercial stabilized formulation) when inhaled 6 hr/day, 5 days/week for 12 months followed by an observation period of up to 19 months produced a statistically significant increase in tumors in Sprague-Dawley Spartan substrain rats when compared to control rats. Hematology and urinalysis were done at 12 and 24 months. No histopathology was done during exposure, at its termination, or at interim periods before natural death or sacrifice at 31 months. At the end of the experiment, 30 different tissues were examined for each animal. The only tumor observed in higher incidence was adrenal pheochromocytoma in female rats and only at the low exposure level. Increased mortality occurred in male rats at the high dose level.

Van Duuren et al. (1979) have summarized the results of a carcinogenicity study using 15 olefinic/aliphatic hydrocarbons including tetrachloroethylene. The compound was tested as an initiator, as a promoter of carcinogenesis, and as a complete carcinogen by repeated skin application to ICR/Ha Swiss mice of both sexes. Tetrachloroethylene was not included in the group of halohydrocarbons that were additionally dosed orally and subcutaneously. Tetrachloroethylene tested negative for initiation/promotion; after a total dose of 163 mg, four of seven mice had papillomas, the first of which appeared at 229 days. Treatment with the tumor promoter only (phorbol myristate acetate 2.5 ug) gave 9 of 10 mice papillomas in 141 days minimum. No distant tumors resulted from the skin application.

In vitro cell transformation techniques are being developed as possible screening techniques for carcinogens. The science has not as yet reached such a stage of sophistication that it can be stated unequivocally that a substance inducing transformation of cells in culture with subsequent induction of a tumor when injected into animals is a carcinogen in vivo. However, a positive result in these transformation assays does offer cause for concern. Price, et al. (1978) tested four chlorinated hydrocarbons in a Fischer rat embryo cell system (F1706) that had previously been shown to be sensitive to other chemical carcinogens. Tetrachloroethylene, trichloroethylene, methyl chloroform and dichloromethane all were shown to be transforming agents. Embryonic cell cultures were exposed to two minimally toxic concentrations of each chemical for 48 hours, then held for two weeks or subdivided 1:2 weekly to provide two new sets of culture, one for the holding series and one for subdivision. Transformation was characterized by the appearance of progressively growing foci made up of cells lacking contact inhibition and orientation and by the growth of macroscopic foci when inoculated into semisolid agar four subcultures after treatment. The ability to produce tumors was shown by the induction of progressively growing tumors at the site of subcutaneous inoculation of 1 million transformed cells into newborn Fischer rats.

Table IX-1

Drinking Water Concentrations and Estimated Excess Cancer Risk

Excess Lifetime Cancer Risk	Range of Concentrations(ug/l)[a]		
	CAG[b]	CAG[c]	NAS[d]
10^{-4}	90	65.8	350
10^{-5}	9	6.6	35
10^{-6}	0.9	0.7	3.5
0	0	0	0

[a] Assumes 2 liters of water consumed/day by 70 kg adult over a lifetime; number represents 95% upper bound confidence limit

[b] (U.S. EPA, 1980)

[c] (Anderson, 1983)

[d] (NAS, 1977;1980)

VIII. MECHANISMS OF TOXICITY

Carcinogenicity

Tetrachloroethylene has been shown to produce liver tumors in mice, but not in rats (NCI, 1977). The reason for this difference is not fully understood at this time. Repetition of the gavage bioassay in 4 rat strains and one mouse strain, and the inhalation bioassay in one rat and one mouse strain may help to resolve this problem.

Henschler and his co-workers, over the past several years, have postulated that the reactivity of metabolically formed epoxide intermediates determine the potential for mutagenicity and carcinogencity. Substances such as vinyl chloride which have unsymmetrically substituted chlorine atoms form more active intermediates, and thus should be mutagenic and carcinogenic. Substances, such as tetrachloroethylene, which have balanced substitution should not be expected to be mutagenic or carcinogenic. Thus far, no convincing evidence exists to suggest that PCE is a mutagen, but the results of the 1977 NCI bioassay do show it to be a murine carcinogen.

A partial explanation for the discrepancy may exist in the results of studies by Pegg, et al. (1979) and Schumann, et al. (1980). These investigators showed that the B6C3F1 mouse used in the bioassay metabolizes significantly more of a dose of PCE than does the Sprague-Dawley rat (7-8 times more PCE/kg body weight following a 10 ppm 6 hour inhalation exposure or nearly twice the amount after a 500 mg/kg oral dose). The greater amount of reactive metabolite(s) in the mouse, whether as the oxide and/or the acyl chloride, would result in a greater degree of complexing with tissue macromolecules and greater opportunity for the manifestation of a carcinogenic response.

At 10 ppm, 63 percent of the total recovered radioactivity from the mouse appeared in the urine as nonvolatile metabolite(s) with a total of 88% of the dose being metabolized and 12 percent was excreted unchanged in expired air (19 and 68 percent, respectively, for the rat (Pegg, et al, 1979). The mouse metabolized 7 to 8 times more PCE per kg of body weight than did the rat following 10 ppm and 1.6 times at 500 mg/kg. Approximately 7 to 9 times more radioactivity was irreversibly bound to hepatic macromolecules in the mouse than in the rat at all exposure levels. No radioactivity was detected bound to purified hepatic DNA at times of peak macromolecular binding in the mouse. These results support the view that mice are more sensitive than rats to the hepatic effects of PCE due to greater metabolism of PCE to (a) reactive intermediates.

Tetrachloroethylene has been studied in several short-term assay systems, most of which evaluate the mutagenic potential of the compound and/or its potential for interaction with DNA. The results of these studies are summarized in Table VII-1. Positive results in certain of these test

Nephrotoxicity

Kidney damage has been observed following PCE exposures of all durations if the dose is high enough. The doses required to induce renal changes exceed those causing hepatic damage. Klaassen and Plaa (1966) observed that renal effects in mice occurred only at near lethal acute doses, whereas hepatic damage was observed at lower levels. In dogs, Klaassen and Plaa (1967), the ED_{50} for elevation of SGOT (an indicator of liver damage) was 0.74 ml/kg i.p. while the ED_{50} for the diminution of PSP clearance (an indicator of kidney damage) was 1.4 ml/kg i.p. Case reports of accidental or workplace exposures suggest that the same relationship probably exists for the human (Coler and Rossmiller, 1953; Hughes, 1954; Lob, 1957; Meckler and Phelps, 1966; Stewart, 1969; Soland, 1967; Trense and Zimmerman, 1969; Hake and Stewart, 1977).

No studies have been reported that consider the question of the mechanism of nephrotoxicity. However, it is quite possible that the same process occurs in the kidney as in the liver, that is, complexing of reactive metabolites with tissue macromolecules, resulting in tissue necrosis. The origin of the reactive metabolite(s) could be the liver, since this/these substance(s) have a survival time of at least several minutes and theoretically could circulate throughout the body. Secondly, the reactive intermediates could be produced from the parent compound _in situ_, as the kidney does possess the mixed function oxidase enzyme system necessary for the metabolism of the compound. However, the quantity of enzymes present in the kidney is less than that found in the liver.

Neurotoxicity

As was discussed in the section of toxicity, tetrachloroethylene manifests its initial observable effects on the central nervous system. All of the symptoms are indicative of varying degrees of depression of function. Few data are available on the possible mechanism by which this CNS depression occurs; however, alteration of the excitability of the neuronal membrane is likely to be involved.

A Russian study by Dmitrieva and Kuleshov (1971) reported alterations in the EEG pattern of rats exposed to low levels of tetrachloroethylene by inhalation over a five month period. After a brief period of increased excitability at the beginning of the study, subsequent changes reflected reduced excitability and lability of the cerebral cortical areas under investigation, with a reduced functional state of the entire CNS and inhibition of activity by the end of the exposure period.

Case reports of chronic exposure to tetrachloroethylene in humans suggest that irreversible neurological damage may occur. However, no histopathological confirmation of the posible nature or site of the lesions has been reported. Dmitrieva and Kuleshov (1971) reported that a few cells of the cerebral cortex of rats showed swelling and vacuolized protoplasm; most cells were normal, however.

Cardiac sensitization

Epinephrine, a compound released from the adrenal medulla, particularly in stress, has a variety of cardiovascular effects. The main effects are vasoconstriction and increases in heart rate, cardiac output and blood pressure. Many hydrocarbons, particularly halogen-substituted hydrocarbons, are known to sensitize the heart to the effects of epinephrine. Among the most dangerous effects is ventricular fibrillation resulting from epinephrine-induced arrhythmia (Reinhardt et al., 1971; Hays, 1972; Reinhardt et al., 1973; Aviado et al., 1976).

The effects of tetrachloroethylene on cardiac sensitization were investigated by Reinhardt et al. (1972). Beagles were injected with epinephrine (0.008 mg/kg intravenously) followed by inhalation of tetrachloroethylene (for five minutes), and then a challenge injection of epinephrine (0.008 mg/kg intravenously). Concentrations of tetrachloroethylene up to 1% by volume (10,000 ppm) failed to produce cardiac sensitization to epinephrine, although 5,000 ppm methyl chloroform produced marked sensitization in some of the dogs. The depressive effect of tetrachloroethylene on the central nervous system precluded further testing at higher concentrations.

The effects of endogenously-released (stress-induced) epinephrine and the effects of injected epinephrine have both been experimentally investigated for effects on the hearts of the dog. There is a species difference with regard to cardiac sensitivity between dogs and primates that was noted in inhalation studies by VanStee and Back (1969), with the dog much more prone to cardiac arrest and ventricular fibrillation at doses that have only transient effects on monkeys and baboons. This difference may have importance when assessing the hazard to man based upon data obtained from dog experiments. However, the arrhythmic response to epinephrine has not yet been completely defined and the role of tetrachloroethylene at the molecular level is little understood. The more sensitive animal models are probably desirable because extra-olation of their data to man offers a better safety margin than use of data from the more resistant species.

Lob (1957) reported that a worker exposed chronically to tetrachloroethylene experienced nausea, vomiting, a feeling of inebriation and fainting. He died when, after reexposure to the chemical, he was given an injection of phenylephrine hydrochloride. It has been recommended that epinephrine or phenylephrine not be used to improve blood pressure (Von Oettingen, 1964), due to the possible cardiac sensitization.

Synergism/Antagonism: Multiple Chemical Exposure

Since PCE is metabolized by mixed function oxidases, compounds which alter the functional activity of the MFO system might be expected to affect its toxicity. Cornish, et al. (1973), however, were unable to demonstrate that phenobarbital pretreatment was capable of modifying the hepatotoxicity of PCE. Moslen et al. (1977) and Reynolds and Moslen (1977) report that PCE produces vacuolization of rough endoplasmic reticulum and increases in serum glutamate oxalacetate transaminase activity following Aroclor 1254 induction of mixed function oxidases. It must be kept in mind that only a small percent of retained PCE is metabolized when compared to other members of the chloroethylene series (Ogata, et al. 1971). Consequently, the experiments conducted by Cornish, et al. (1973), Moslen, et al. 1977) and Reynolds and Moslen (1977) were of too short a duration to fully assess the influence of metabolism on the long-term toxicity of PCE.

Intolerance of alcohol has been reported with PCE exposure (Gold, 1969). As both compounds are central nervous system depressants, such effects are to be expected. There do not appear to be any documented metabolic interactions of PCE with alcohol as there are with trichloroethylene (Cornish and Adefuin, 1966; Gessner, 1973).

Under conditions that enhanced the toxicity of carbon tetrachloride and trichloroethylene, Cornish and Adefuin (1966) administered ethanol to rats 16 to 18 hours before exposing them to tetrachloroethylene. Exposures were at 4,000 ppm (6 hours), 5,000 ppm (4 hours), 10,000 ppm (2 hours) and 15,000 ppm (2 hours). Serum enzymes SGOT, SGPT, and isocitric dehydrogenase, liver lipids and histology of liver, kidney, lung, adrenal and spleen were studied. Alcohol ingestion did not potentiate the toxicity of tetrachloroethylene in any of these parameters at the levels studied.

Potential synergistic effects of tetrachloroethylene with diazepam or ethanol were measured in six male and six female subjects, utilizing a battery of behavioral and neurological tests (Stewart, et al., 1977). The behavioral test battery included: Michigan eye-hand coordination, rotary pursuit, Flanagan coordination, Saccade eye velocity and dual-attention tasks. In addition, the electroencephalogram was recorded during the exposure to tetrachloroethylene.

The subjects were exposed, by inhalation, to tetrachloroethylene at levels of 0, 25 or 100 ppm for 5.5 hours. Two, four and six hours after the initiation of exposure to PCE, they also received either 0, 6 or 10 mg/day diazepam or 0, 0.75 or 1.51 ml/kg body weight 50% ethanol.

Data analysis revealed that subjects had decreased performance on at least one test while on each drug alone at the highest dose level, but no synergistic interaction with tetrachloroethylene was seen in any test with either drug. Alcohol consumption decreased performance in three of the tests. Diazepam showed significant performance effects only on the rotary pursuit test. Tetrachloroethylene, at 100 ppm, repeatedly gave decreased performance only on the Flanagan coordination test. This 7-min test is designed to assess memory together with two related forms of manual dexterity (Buros, 1972).

Since PCE is metabolized to trichloroacetic acid, there may be a possibility of its acting synergistically with compounds, such as warfarin, that bind significantly to serum albumin (Wardell, 1974). Although this phenomenon has been suggested for trichloroethylene (Ertle, et al. 1972), this possibility has not been investigated systematically with PCE.

PCE interactions with benzene or toluene have been studied systematically with lethality as an endpoint (Withey and Hall, 1975). Mixtures were combined in the following ratios: 100:0, 80:20, 60:40, 40:60, 20:80 and 0:100. Intubation of rats with mixtures of benzene and PCE yielded a combined toxicity which was only slightly less than additive. Mixtures of toluene and PCE resulted in LD_{50} values of less than that predicted for simple additivity, indicating synergistic effects.

The inhalation toxicity of a solvent containing 25% tetrachloroethylene and 75% methyl chloroform was determined by Rowe et al. (1963) in guinea pigs and rabbits. Synergism was not seen in these experiments because the LC_{50} plot of the mixture superimposed upon the LD_{50} plot the data for each separate constituent. Death resulted from respiratory failure. Gross examination of the parenchymatous organs revealed only mild effects on the liver and kidneys. Application of the solvent to ocular membranes of the rabbits resulted in a response interpreted as pain and slight conjunctival irritation which cleared within 48 hours. Rats exposed in single inhalation experiments exhibited central nervous system depression. Minor liver changes occurred with longer term (six months) exposure. Rats died acutely from either cardiac or respiratory failure. The single oral dose LD_{50} in rats was 5.7 to 14.8 g/kg. The single inhalation toxicity for rats (LC_{50}) was also low: exposures for 0.5, 1.0, 2.0, 4.0, and 7.0 hours were required for concentrations of 24,000, 20,000, 16,500, 14,000 and 12,000 ppm, respectively. Inhalation toxicity studies with the solvent mixture showed guinea pigs to be the most sensitive to the tetrachloroethylene/methyl chloroform mixture.

Rowe et al. (1963) also exposed rabbit skin to the solvent mixture (nine exposures in 11 days) and found the toxicity of the mixture to be no greater than that which would be expected from its constituents. Exposure of the skin to the chemical mixture resulted in slight erythema and exfoliation, the response being greater when the skin was abraded and the solvent-soaked pad bandaged to the skin. However, healing was complete and without scarring.

Smyth et al. (1949) studied the potential for synergistic action of tetrachloroethylene and 26 other solvents administered orally in all possible combinations to rats. The results followed a predictive additive toxicity model except for the data on polyethylene glycol 400, butyl ether, dioxane and acetophenone. These four substances showed greater than additive toxicity when given with PCE.

High Risk Groups/Susceptible Population

No reports were found in the scientific literature which identify any subgroup of the human population which may be more susceptible to or at greater risk from exposure to tetrachloroethylene. However, one could generalize and state that individuals suffering from preexisting disease in any of the target organs for PCE toxicity, especially the central nervous system, liver, kidney or skin, but, also perhaps, the immune system, might be expected to manifest adverse health effects at levels of PCE exposure lower than those which would induce adverse effects in the "normal" population.

IX. Quantification of Toxicological Effects

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Adjusted Acceptable Daily Intake (AADI) for the chemical is determined. For ingestion data, this approach is illustrated as follows:

$$\text{Adjusted ADI} = \frac{(\text{NOAEL or MEL in mg/kg})(70\ \text{kg})}{(\text{Uncertainty factor})(2\ \text{liters/day})}$$

The 70 kg adult consuming 2 liters of water per day is used as the basis for the calculations. A "no-observed-adverse-effect-level" or a "minimal-effect-level" is determined from animal toxicity data or human effects data. This level is divided by an uncertainty factor because, for these numbers which are derived from animal studies, there is no universally acceptable quantitative method to extrapolate from animals to humans, and the possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human toxicity data, an uncertainty factor is used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxins. The guidelines set forth by the National Academy of Sciences (Drinking Water and Health, Vol. 1, 1977) are used in establishing uncertainty factors. These guidelines are as follows: an uncertainty factor of 10 is used if there exist valid experimental results on ingestion by humans, an uncertainty factor of 100 is used if there exist valid results on long-term feeding studies on experimental animals, and an uncertainty factor of 1000 is used if there exists scanty results on experimental animals.

In the quantification of carcinogenic effects, mathematical models are used to calculate the estimated excess cancer risks associated with the consumption of a chemical through the drinking water. EPA's Carcinogen Assessment Group have used the multistage model, which is linear at low doses and does not exhibit a threshold, to extrapolate from high dose animal studies to low doses of the chemical expected in the environment. This model estimates the upper bound (95% confidence limit) of the excess cancer rate that would be expected to occur at a specific exposure level for a 70 kg adult, consuming 2 liters of water per day, over a 70 year lifespan. Excess cancer rates can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There exists no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude. The multi-stage model often gives the highest risk estimate and thus would usually be the one most consistent with the conservative regulatory philosophy.

The scientific data base, which is used to support the setting of risk rate levels as well as other scientific endeavors, has an inherent uncertainty. This is due to the fact that it is not possible to measure a quantity with 100%

accuracy because the tools of scientific measurement by their very nature involve both systematic and random error. In addition, in many areas there is limited knowledge concerning the health effects of contaminants in drinking water, and in all areas uncertainty exists. When developing risk rate levels, several other areas of uncertainty exist such as the effect of age, sex, species and organ of the test animals used in the experiment, and the rate of exposure of the test animals or humans. The dose-response data is usually known at high levels of exposure, with no information being available at the levels of exposure for which a standard is being set. In most cases, data only exists for animals and thus uncertainty exists when the data is extrapolated to humans. Additional uncertainty exists when there is exposure to more than one contaminant due to the lack of information about possible synergistic and antagonistic effects.

Non-carcinogenic Effects

The principal non-carcinogenic toxic effects of tetrachloroethylene in humans and other animals from both acute and longer-term exposures at relatively high doses include central nervous system (CNS) depression and fatty infiltration of the liver and kidney with concomitant changes in serum enzyme activity levels indicative of tissue damage. The appearance and intensity of these and other adverse effects are dependent upon dose and duration of exposure. Death following high level acute exposures usually results from the CNS effects. Delayed fatalities after these high exposures usually due to hepatic and renal effects.

No information exists on the possible existence of any subgroup of the population which is more likely to be susceptible to the toxic effects of tetrachloroethylene, except for the case history of the woman who suffered asthmatic attacks following minimal exposure to PCE in a dry cleaners after having suffered a previous attack subsequent to extended exposure to the substance.

Enhancement of the toxicity of PCE does not occur following prior exposure to phenobarbital or alcohol, each of which is an enhancer of mixed function oxidase enzyme system activity. No synergism occurs during concomitant exposure to PCE and diazepam or methyl chloroform. LD_{50} determinations for mixtures of benzene and PCE or toluene and PCE yielded less than additive toxicity.

Oral exposures of rats to PCE and 26 other solvents in all paired combinations revealed additive toxicity, except for polyethylene glycol 400, butyl ether, dioxane and acetophenone which were synergistic.

The oral 24-hour LD_{50} in mice ranges from 6.5-8.0 g/kg in oil (Kohne, 1940) to 8.8-10.8 g/kg (Dybing and Dybing, 1946; Wenzel and Gibson, 1951). The inhalation 24-hour LC_{50} in mice after 4 hours' exposure is about 5200 ppm (35,000 mg/m^3) (Friberg, et al., 1953) and the intraperitoneal 24-hour LD_{50} is 4.7 g/kg (Klaassen and Plaa, 1966). In rats, the oral LD_{50} is 13 g/kg (Smyth, et al., 1969); the inhalation LD_{50} after 4 hours' exposure is 4000 ppm (27,000 mg/m^3) (Carpenter, et al., 1949).

In dogs, the intraperitoneal 24-hour LD_{50} is 3.4 g/kg (Klaassen and Plaa, 1967).

Effects after non-fatal short-term or subchronic exposures are manifested principally as transient CNS depression and/or damage to the liver and kidney. Klaassen and Plaa (1966, 1967) showed that single high doses to rats and dogs resulted in elevated serum SGOT levels and BSP retention, indicative of liver and kidney damage, respectively. Single oral doses of 2,158 mg/kg to rabbits resulted in mild, transient elevation of several serum enzyme activities reflective of liver effects (alkaline phosphatase, SGOT, SGPT) (Fujii, 1975). Single intraperitoneal doses of 50-330 mg/kg tetrachloroethylene to rats yielded SGOT activity increases of 20-44% (Cornish, et al., 1973). Kylin, et al. (1963) noted a dose-response-related increase in fatty infiltration of the liver of mice after four hours' exposure to 200-3,000 ppm via inhalation. Decreased hepatic ATP and increased total lipid and triglyceride levels were observed in mice exposed to 800 ppm in air for 3 hours (Ogata, et al., 1968).

Rowe, et al. (1952) exposed rats to 1,600 ppm, 7 hours/day, 5 days/week 18 times over 25 days. Not only did they observe CNS depression which could be antagonized with atropine, suggesting a cholinergic response, but,. at autopsy, the animals exhibited hepatic and renal hypertrophy. Guinea pigs, under the same dosing regimen, also exhibited hepatic hypertrophy as well as centrolobular degeneration. No effects were apparent in rats exposed at levels up to 400 ppm; however, these changes also were observed in guinea pigs at 200 and 400 ppm, but not at 100 ppm. Kylin, et al. (1965) observed fatty infiltration in livers of mice exposed to 200 ppm, 4 hours/day, 5 days/week for 8 months. Rabbits showed liver enzyme changes and renal function alterations following 200-300 ppm exposures, 4 hours/day, 5 days/week for 9 weeks (Mazza, 1972; Brancaccio, et al., 1971). There are no subchronic oral exposure studies available at this time.

Additional changes which have been reported, primarily in the foreign literature, include morphological changes in mast cells, alteration in serum protein ratios and other indicators of immune system effects, a decrease in brain RNA along with an increase in brain non-specific cholinesterase activity, other subtle behavioral and neurological effects, degeneration of the epithelium of the testis and congestion of the spleen. These changes were reported in studies of unconfirmed validity, but which demand consideration when evaluating the overall toxicity of this compound, especially since some of these effects were noted at relatively low exposure levels over extended exposure periods (as low as 15 ppm for 3 months (Dmitrieva, 1968)). Confirmation of these changes purported to have occurred at these low levels of exposure should be made through additional research.

The only chronic oral exposure study reported with tetrachloroethylene to date is the first NCI bioassay in which Fischer 344 rats and B6C3F1 mice were gavaged with daily doses of 400 mg/kg/day or greater for 78 weeks (NCI, 1977). In addition to the increased incidence of tumors noted in the mice, animals of both sexes of both species exhibited a very high incidence of toxic nephropathy (60% or higher). The results of this study do not allow for the derivation of a no-observed-adverse effect level (NOAEL). All other longer-term or chronic studies performed with tetrachloroethylene employed the inhalation route.

Carpenter (1937) exposed rats of both sexes to 70 ppm (475 mg/m^3), 230 ppm (1,560 mg/m^3) or 470 ppm (3,200 mg/m^3), 8 hours/day, 5 days/week for 150 days. No significant changes were observed at the lowest dose. At 230 ppm, renal congestion and swelling were noted. At 470 ppm, the liver also was congested and exhibited cloudy swelling, changes which remained 46 days after termination of exposure. The kidney showed increased secretion, cloudy swelling and desquamation; the spleen was congested and showed an increase in pigment content. The results of this study suggests a NOAEL of 70 ppm (475 mg/m^3). An acceptable daily intake (ADI) could be derived thusly:

$$\frac{475\ mg/m^3 \times 1\ m^3/hr \times 8\ hrs \times 5 \times 0.5}{100 \times 10 \times 7} = 1.36\ mg/day$$

(or .02 mg/kg/day for a 70 kg adult)

Where: 475 mg/m^3 (70 ppm) = NOAEL

1 m^3/hr = ventilation volume for 70 kg adult

8 hrs = duration of exposure/day

5/7 = conversion of 5 days/week exposure to 7 day/week exposure

0.5 = ratio of dose absorbed (experimentally-derived)

100 = uncertainty factor, appropriate for application to NOAEL in animal with no equivalent data in the human (longer-term exposure duration)

10 = uncertainty factor, appropriate for exposure duration significantly less than lifetime

Rowe, et al. (1952) exposed rats, guinea pigs, rabbits and monkeys to tetrachloroethylene via inhalation at 400 ppm (2,720 mg/m^3) and guinea pig only at 100 ppm (680 mg/m^3) or 200 ppm (1,360 mg/m^3), 7 hours/day, 5 days/week for periods up to 250 days. Guinea pigs (8 per sex per group) were the most sensitive to the adverse effects of this substance. At 100 ppm, after 132 exposures, the only changes noted were an increase in liver weight in the females and mild fatty deposition in the centrolobular areas of the liver in a few males and all of the females. At 200 ppm, there was a significant decrease in growth rate and increase in liver weight of the females. Total lipid and esterified cholesterol levels in the liver also increased. In addition, light central fatty degeneration without cirrhosis was observed. At 400 ppm, rats, rabbits and monkeys showed no significant changes, while the guinea pigs continued to exhibit the changes observed at 200 ppm, but of somewhat greater magnitude. The liver changes consisted of moderate fatty degeneration and slight cirrhosis.

Applying the philosophy of using results from the most sensitive species to establish allowable levels for the human, one would use the data gathered in the guinea pig to establish an ADI from this study. No NOAEL can be identified but a MEL (Minimum Effect Level) of 100 ppm can be used. An ADI based upon these data could be derived as follows:

$$\frac{678\ \text{mg/m}^3 \times 1\ \text{m}^3\text{/hr} \times 7\ \text{hr} \times 5 \times 0.5}{1000 \qquad \times \qquad 7} = 1.7\ \text{mg/day}$$

(or 0.025 mg/kg/day for a 70 kg adult)

Where: 678 mg/m^3 (100 ppm) = MEL

1 m^3/hr = ventilation volume/hour in 70 kg adult

7 hr = exposure period/day

5/7 = conversion of 5 day/week exposure pattern to 7 day/week pattern

0.5 = ratio of dose absorbed (experimentally-derived)

1000 = uncertainty factor, appropriate for application to MEL in animals with no equivalent data in the human (longer-term exposure duration)

A series of studies reported effects at very low exposure levels for longer periods of time in several species. It is often difficult to interpret these results because of the investigators' reporting methods; also, the awkwardness of translations into English make for uncertainty. Nonetheless, it is difficult to ignore these data because there show a dose-reponse and NOAELs can be identified for sensitive end-points of toxicity.

In these reports, Dmitrieva and Kulshov (1971) reported aberrancies in the EEGs of rats exposed 5 hrs/day for 5 months to 15 ppm (100 mg/m^3) tetrachloroethylene. Some histopathology also was noticed in the cerebral cortex. Navrotskii, et al. (1971) described adverse effects on the immune system, certain blood components and liver morphology of rabbits exposed via inhalation, 3-4 hours/day, for 7-11 months at levels of 15 ppm (100 mg/m^3), but not at 1.5 ppm (10 mg/m^3). And, finally, Schmuter (1972) reported significant changes in antibody production to a Salmonella typhosa antigen challenge in chinchillas exposed at 15 ppm (100 mg/m^3), 3 hours/day, 6 days/week for 8-10 months, with fewer changes observed at 1.5 ppm.

Rampy, et al. (1978) exposed Sprague-Dawley rats to 0, 300 or 600 ppm commercial grade tetrachloroethylene 6 hours/day, 5 days/week for 12 months, followed by observation for their lifetime or up to 31 months. In this unpublished report, the authors observed no significant changes in animals exposed at 300 ppm. At 600 ppm there was an increase in mortality in males which the investigators attributed to "an earlier onset of spontaneous advanced chronic renal disease." There were increases in the numbers of inflammatory cells in the kidney with focal progressive nephrosis in solvent-exposed rats of both sexes, at both doses, with greater numbers at the higher dose. These cases apparently did not reach statistical significance, however.

Some might argue that this study could be useful in deriving a NOAEL for tetrachloroethylene. However, the protocol used has a major flaw in it which renders it unusable for this purpose. No sacrifices were performed during the course of the 12-month exposure period or at its termination except for the three animals per sex group sacrificed at the termination of exposure for use in the cytogenetics study. It would have been particularly important to have a histopathological profile of a representative sampling during and at the termination of exposure, especially since other investigators have reported liver and kidney changes at equivalent dose levels which are reversible after cessation of exposure. It is quite possible that non-fatal adverse changes could have occurred during the exposure period which would have completely reverted to normal by the time of death or terminal sacrifice at 31 months. In addition, had exposure been continued to the time of sacrifice at 31 months, the pathology may have been enhanced to a point where it compromised the health of the animals in an adverse manner.

Quantification of Non-carcinogenic Effects

The effects of tetrachloroethylene in humans are essentially identical to those observed in animal experiments. As has been pointed out, no acceptable dose-response data are available after exposure via ingestion. Thus, we will consider the inhalation data when quantifying non-carcinogenic effects.

The series of studies reported from the Eastern bloc identify effects observed at the lowest levels of exposure. In these studies, a variety of effects are noted, including those afecting the central nervous system, at exposures as low as 15 ppm (100 mg/m^3), but not at 1.5 ppm (10 mg/m^3). NOAELs can be identified from these studies whereas no NOAEL can be established from the Rowe study. In addition, the NOAELs identified in this series of studies are at levels lower than those identified in the Carpenter study. For these reasons, we have selected the Eastern bloc studies to serve as the basis for the development of the Adjusted ADI for tetrachloroethylene.

If we were to assume that these studies were appropriate for use in developing an acceptable daily intake (ADI) for non-carcinogenic effects, then the ADI would be derived as follows:

$$\frac{10\ \mathrm{mg/m^3} \times 1\ \mathrm{m^3/hr} \times 4\ \mathrm{hr/day} \times 6 \times 0.5}{100 \times 7} = 0.17\ \mathrm{mg/day}$$

(or 0.0025 mg/kg/day for a 70 kg adult)

Where: 10 mg/m^3 = NOAEL

1 m^3/hr = ventilation volume for a 70 kg adult

4 hr/day = exposure period/day

6/7 = conversion of 6 day/week exposure period to daily exposure period

0.5 = ratio of dose absorbed (experimentally-derived)

100 = uncertainty factor, appropriate for use with NOAEL from animal study with no comparable human data (longer-term exposure duration)

The Adjusted ADI, derived to reflect allowable daily exposure of a 70 kg adult drinking two liters of water per day, and whose sole source of exposure to tetrachloroethylene is via that drinking water, would be:

$$\frac{\mathrm{ADI}}{2\mathrm{l/day}} = \frac{0.17\ \mathrm{mg}}{2} = 0.085\ \mathrm{mg/l}$$

This calculation does not reflect the potential carcinogenic risk.

Carcinogenic Effects

Tetrachloroethylene was tested for carcinogenic potential in B6C3F1 mice and Fischer 344 rats in the NCI Bioassay Program (NCI, 1977). In those bioassays, the test compound, containing a small amount of stabilizer, was administered in oil by gavage 5 days/week for 78 weeks. Under the experimental conditions employed in the studies, it was shown that tetrachloroethylene caused a significant increase in the incidence of hepatocellular carcinomas in both sexes of mice at both dose levels when compared with the untreated and the vehicle control groups. In the rats, there appeared to be no significant increased incidence of neoplastic lesions at any site. The implications of these results must be tempered by the fact that, among the rats, there were high incidences of respiratory disease in all groups, high incidences of toxic nephropathy in the tetrachloroethylene-treated groups and a higher mortality rate among the treated groups than the control groups. Because of this difference in mortality rates, there exists the possibility that the results could have been different if survival had been equivalent in all groups.

For a variety of reasons, it was decided that the bioassay would be repeated. Gavage studies in one mouse and four rat strains and one inhalation study in one rat and one mouse strain were planned. The dosing and histopathology have been completed or soon will be. Hopefully, the data from these studies will be available for incorporation into the tetrachloroethylene RMCL development process.

The unpublished inhalation study by Dow Chemical Company (Rampy, et al., 1978) was designed to examine the carcinogenic potential of tetrachloroethylene by this route of exposure. The investigators reported that neither the 300 nor the 600 ppm dose (given 6 hr/day, 5 days/week for 12 months) produced any statistically significant increases in neoplastic lesions at any site in Sprague-Dawley rats of either sex. For the same reasons stated above in the section on non-carcinogenic effects, this study is not suitable for consideration in the evaluation of the carcinogenic potential of tetrachloroethylene.

Tetrachloroethylene has been shown to be carcinogenic by the oral route in mice only to date(NCI, 1977) However, this is the same route by which individuals would be exposed to this substance when it is present in their drinking water. Therefore, one must determine whether or not a carcinogenic risk exists to the human, and, if so, estimate the magnitude of that risk to individuals drinking water which contains measurable levels of this substance.

On the basis of the data reported in the NCI bioassay published in 1977, IARC (1979) concluded that there is limited evidence to state that it is a carcinogen in the mouse. Chemicals which fall into this category or classification by this Agency are usually there for two reasons. Firstly, the experimental data may be restricted such that it is not possible to determine a causal relationship between exposure and development of a lesion. Secondly, certain neoplasms, such as lung adenomas and hepatomas in mice, are considered of lesser significance than tumors of other types occurring at other sites. In addition, some chemicals for which that there is limited evidence of carcinogenicity in animals have also been studied in humans with, in general, inconclusive results. Thus far, we have no substantial evidence that shows that tetrachloroethylene is a human carcinogen. The epidemiology studies done to date, which offer suggestive evidence, are either incomplete or inadequate for judging the carcinogenic potential of this compound in the human.

Quantification of Carcinogenic Effects

Using methodology described in detail elsewhere (USEPA, 1980), the EPA's Carcinogen Assessment Group (CAG) has calculated estimated incremental excess cancer risk associated with exposure to tetrachloroethylene in ambient water, extrapolating from data obtained in the 1977 NCI bioassay in mice with this compound (NCI, 1977). CAG employed a linearized, non-threshold multistage model to estimate the upper bound 95% confidence limit of the excess cancer rate that would occur at a specific exposure level for a 70 kg adult ingesting two liters of water and 6.5 grams of fish and seafood (fish factor) every day over a 70-year lifespan.

The National Academy of Sciences (NAS, 1977;1980) and EPA's Carcinogen Assessment Group (Anderson, 1983) have calculated estimated 95% upper confidence limit incremental excess cancer risks associated with the consumption of tetrachloroethylene via drinking water alone by mathematical extrapolation from the high-dose animal studies. Each group employed the linearized, non-threshold multistage model, extrapolating from data obtained in the 1977 NCI bioassay in mice.

In all three instances, a range of tetrachloroethylene concentrations were computed that would be estimated to increase the risk by one excess cancer per million (10^6), per hundred thousand (10^5) and per ten thousand (10^4) population over a 70-year lifetime assuming daily consumption of 2 liters of water by a 70 kg adult at the stated exposure level. The ranges of concentrations are summarized in Table IX-1.

Table IX-1

Drinking Water Concentrations and Estimated Excess Cancer Risk

Excess Lifetime Cancer Risk	Range of Concentrations(ug/l)[a]		
	CAG[b]	CAG[c]	NAS[d]
10^{-4}	90	65.8	350
10^{-5}	9	6.6	35
10^{-6}	0.9	0.7	3.5
0	0	0	0

[a] Assumes 2 liters of water consumed/day by 70 kg adult over a lifetime; number represents 95% upper bound confidence limit

[b] (U.S. EPA, 1980)

[c] (Anderson, 1983)

[d] (NAS, 1977;1980)

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